3D convolutional neural networks for outcome prediction in glioblastoma using methionine PET and T1w MRI

Iram Shahzadi[1,2,3,4] iram.shahzadi@uniklinikum-dresden.de
Annekatrin Seidlitz[1,2,4,5] Annekatrin.Seidlitz@uniklinikum-dresden.de
Alex Zwanenburg[1,2,4] alexander.zwanenburg@nct-dresden.de
Bettina Beuthien-Baumann[6,7] b.beuthien-baumann@dkfz-heidelberg.de
Ivan Platzek[4,8] Ivan.Platzek@uniklinikum-dresden.de
Jörg Kotzerke[4,6] Joerg.Kotzerke@uniklinikum-dresden.de
Michael Baumann[1,3,5] michael.baumann@dkfz-heidelberg.de
Mechthild Krause[1,2,4,5,9] Mechthild.Krause@uniklinikum-dresden.de
Steffen Löck[1,2,4,5] steffen.loeck@oncoray.de

[1] *OncoRay – National Center for Radiation Research in Oncology, Dresden, Germany*
[2] *German Cancer Consortium (DKTK) partner site Dresden, Germany*
[3] *German Cancer Research Center (DKFZ), Heidelberg, Germany*
[4] *National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany*
[5] *Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany*
[6] *Department of Nuclear Medicine, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany*
[7] *German Cancer Research Center (DKFZ), Department of Radiology, Heidelberg, Germany*
[8] *Institute of Radiology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany*
[9] *Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiooncology, Dresden, Germany*

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Abstract

For treatment personalization of patients with glioblastoma, we investigate three different 3D convolutional neural networks (3D-CNN) for predicting time to recurrence (TTR) and overall survival (OS) from postoperative [^{11}C] methionine PET (MET-PET) and gadolinium-enhanced T1-weighted magnetic resonance imaging (T1c-w MRI). The 3D-DenseNet model on MET-PET integrated with age and MGMT status achieved the best performance on independent test data (Concordance-Index: TTR 0.68, OS 0.65) with significant patient stratification (p-value: TTR 0.017, OS 0.039). After prospective validation, these models may be considered for treatment personalization.

Keywords: Glioblastoma, survival analysis, 3D-CNN, biomarker.

1. Introduction

Patients with glioblastoma (GBM) have a poor prognosis with a high recurrence rate and a 5-year survival probability of 5% after multimodality treatment. Biomarker-based prognosis of time to recurrence (TTR) and overall survival (OS) may help to stratify patients

that can benefit from escalated radiotherapy doses. Elevated tracer uptake of amino acid positron emission tomography (PET) in tumour residuals after surgery may represent such a biomarker (Seidlitz et al., 2021). Therefore, in this study, we leverage the potential of different 3D convolutional neural network (3D-CNN) architectures to extract prognostic information from [^{11}C]-methionine (MET)-PET and T1c-w MRI. Furthermore, we integrate the 3D-CNN predictions with relevant clinical information.

2. Materials and methods

All patients were newly diagnosed with histologically confirmed glioblastoma and underwent radiochemotherapy (RCT) within 7 weeks after surgery. Patients from the PETra trial (Seidlitz et al., 2021) (ethics id. EK41022013) were allocated to the training data (N=85), while patients from the PETra validation trial (ethics id. EK390072021) were allocated to test data (N=47). The considered endpoints TTR and OS were calculated from the first day of RCT to the day of event or censoring. T1c-w images were corrected for background phase variation and bias fields using Canny edge detection and N4ITK, respectively. Standardized uptake values (SUV) above 10 in each MET-PET volume were set to 10 and the entire volume was normalized to [0,1], while intensity values of T1c-w data were z-score normalized. MET-PET and T1c-w images were resampled to an isotropic voxel size. A single image volume centred around the clinical target volume's (CTV) centre of mass was then extracted (MET-PET: $60 \times 60 \times 44$, T1c-w MRI: $80 \times 80 \times 80$ voxels). Three different 3D-CNN architectures, 3D-VGG, 3D-ResNet, and 3D-DenseNet, were trained for both endpoints using Adam optimizer (batch size=16, epochs=300, exponential decay with initial learning rate=1.10^{-4}). Model losses were optimized using a survival-specific loss function for each batch of image volumes, i.e. the negative of the Cox partial log-likelihood. Network training was performed within 5 repetitions of 5-fold cross-validation (CV), stratified by the event status, on the training dataset. A training and validation ensemble prediction was obtained by averaging the outputs of the models in CV folds. For independent testing, 25 trained models were transferred to test data and outputs were averaged. To analyse the impact of image augmentations, image volumes were either used unchanged or augmented depending on the image modality by gamma correction, Gaussian noise and blur, rotation, and mirroring. Finally, clinical/molecular features that were significantly related to outcome in univariable Cox regression on the training data were combined with the ensemble CNN predictions in a multivariable Cox model, which was subsequently validated. Model discrimination was evaluated by the concordance index (CI). Patients were stratified into low and high-risk groups of TTR and OS using an optimal cutoff that was based on the most significant stratification of the training hazard. Stratified patient groups were compared using the log-rank test (significance level 0.05). Our python code (Keras, Tensorflow backend) is publicly available from https://github.com/oncoray/cnn-petra.

3. Results

Table 1 presents the deep-learning results for the prognosis of TTR and OS. For MET-PET, on the test set without data augmentation none of the models was able to stratify patients into high and low-risk groups. With data augmentation, 3D-DenseNet showed

Table 1: Concordance indices (CI) for time to recurrence (TTR) and overall survival (OS) in training, internal validation, and test data. Best performance is marked in bold.

Modality	Model	Augmentation	Endpoint A=TTR B=OS	CI training	CI internal validation	CI test set	p-value test set (log-rank test)
PET	DenseNet	No	A	0.75	0.68	0.60	0.89
			B	0.63	0.59	0.62	0.99
	ResNet	No	A	0.84	0.62	0.63	0.23
			B	0.89	0.58	0.66	0.72
	VGG	No	A	0.85	0.66	0.55	0.55
			B	0.87	0.68	0.48	0.46
	DenseNet	**Yes**	**A**	**0.84**	**0.68**	**0.66**	**0.027**
			B	**0.82**	**0.61**	**0.64**	**0.033**
	ResNet	Yes	A	0.90	0.63	0.61	0.17
			B	0.87	0.55	0.61	0.23
	VGG	Yes	A	0.84	0.69	0.55	0.76
			B	0.88	0.70	0.53	0.43
DenseNet PET+clinical	**Cox**	**Yes**	**A**	**0.85**	**0.74**	**0.68**	**0.017**
			B	**0.82**	**0.69**	**0.65**	**0.039**

the best performance (TTR: CI=0.66, OS: CI=0.64) with significant stratification for TTR (p=0.027) and OS (p=0.033). Integrating the significant clinical features age and MGMT status with these models further improved the performance (TTR: CI=0.68, OS: CI=0.65), Figure 1. For T1c-w MRI, on test set none of the models achieved a significant stratification.

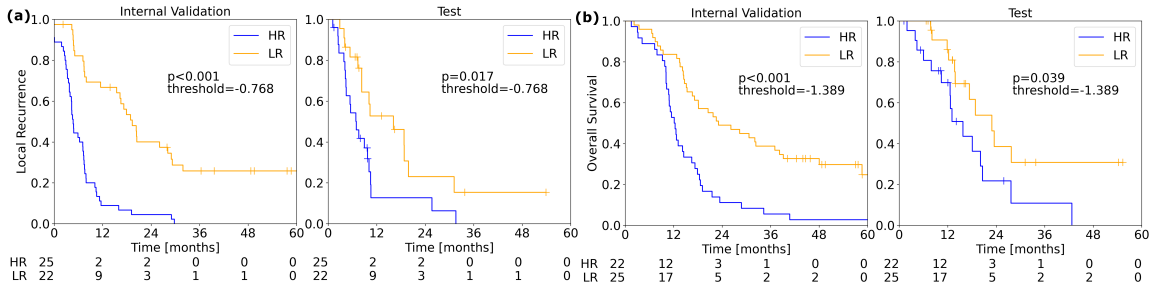

Figure 1: Kaplan-Meier estimates for (a) time to recurrence and (b) overall survival in internal validation and testing based on the respective MET-PET DenseNet model combined with age and MGMT status. HR: High risk, LR: Low risk

4. Discussion

We investigated 3D-CNN models in a survival analysis setting for the endpoint TTR and OS, based on postoperative MET-PET and T1c-w MRI images of glioblastoma patients. Best performance and successful validation was achieved by 3D-DenseNet on augmented MET-PET data integrated with age and MGMT status. Limitations of this study are its limited sample size and the retrospective nature. We conclude that 3D-CNN models that account for spatial relationships between volumetric data can be useful for developing novel biomarkers to achieve the goal of personalized radiotherapy.

References

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