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Noninvasive Characterization of Tumor Angiogenesis and Oxygenation in Bevacizumab-treated Recurrent Glioblastoma by Using Dynamic Susceptibility MRI: Secondary Analysis of the European Organization for Research and Treatment of Cancer 26101 Trial (*Kickingereder et al. Radiology 2020)*

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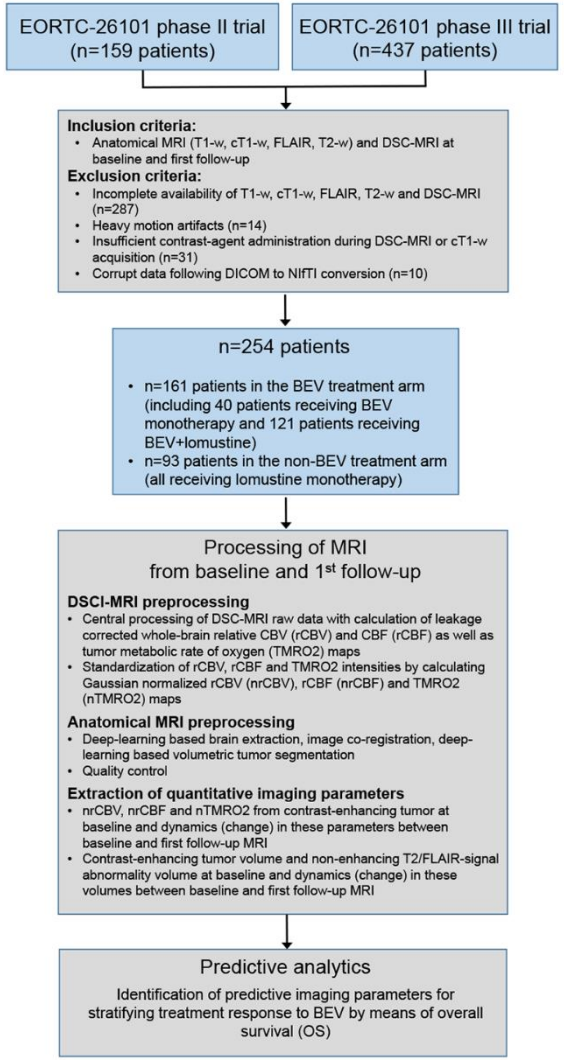
Translational image research in brain tumor clinical trials



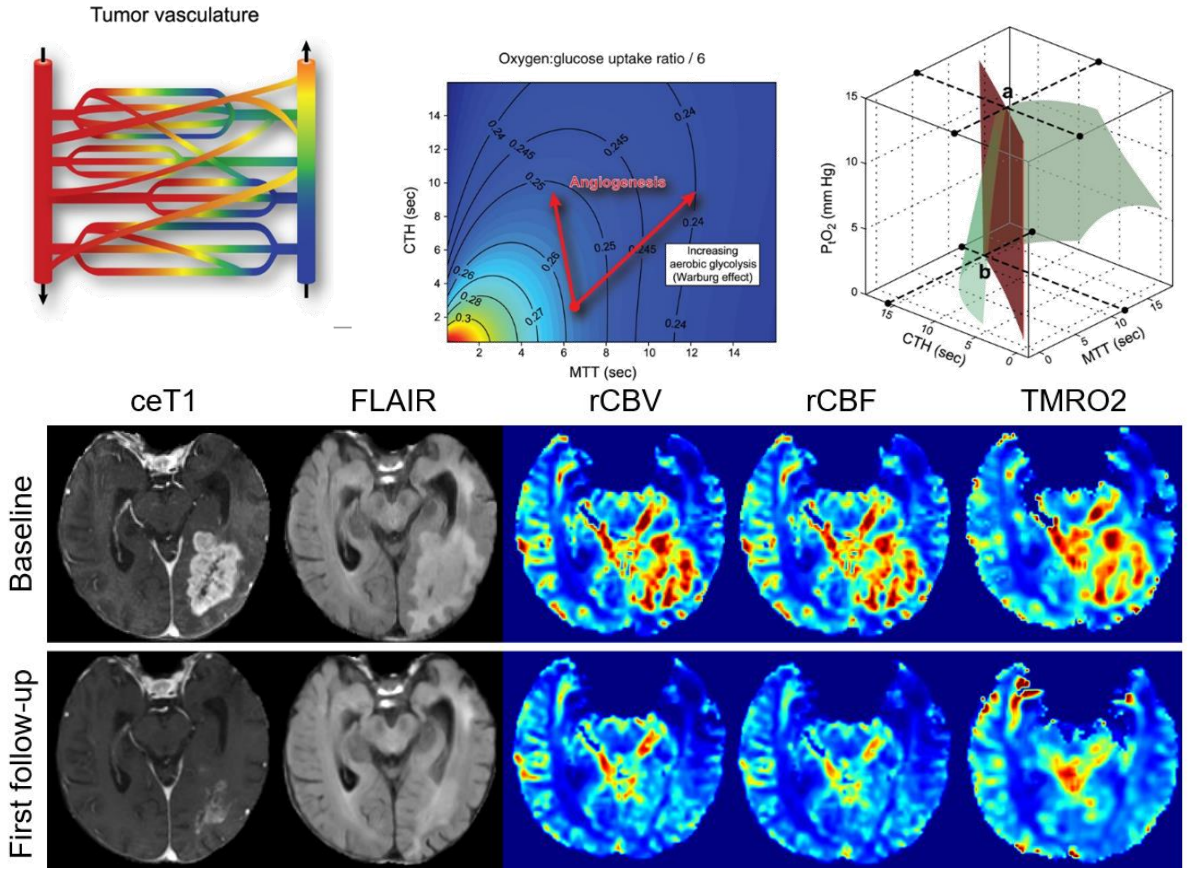
European Organization for Research and Treatment of Cancer (EORTC) 26101 Trial (*Wick et al. N Engl J Med. 2017*)

- Randomized, controlled phase 2 and 3 clinical trial with 596 patients conducted at 37 institutions in Europe
- Randomizing patients for receiving bevacizumab (Avastin®) + lomustine vs. lomustine in patients with glioblastoma at first recurrence
- First brain tumor trial with standardized MRI protocol

Purpose of the secondary analysis of the EORTC-26101 trial (*Kickingereder et al. Radiology 2020*)

- To perform longitudinal characterization of intratumoral angiogenesis and oxygenation by using dynamic-susceptibility contrast agent–enhanced (DSC) MRI and evaluate its potential for predicting outcome from administration of bevacizumab.

Longitudinal characterization of intratumoral angiogenesis and oxygenation by using DSC-MRI



Workflow performed within this study…

- Automated processing of MRI data using deep-learning algorithms (based on Isensee et al. Human Brain Mapp 2019, Kickingereder et al. Lancet Oncol 2019)
- Automated non-invasive quantification of intratumoral angiogenesis (*tumor blod flow and volume [CBF, CBV]*) and oxygenation (*tumor metabolic rate of oxygen [TMRO2]*) from DSC-MRI (based on Ostergaard et al. Cancer Res 2013)
- Predictive analytics (assocation of imaging biomarkers with study endpoints)

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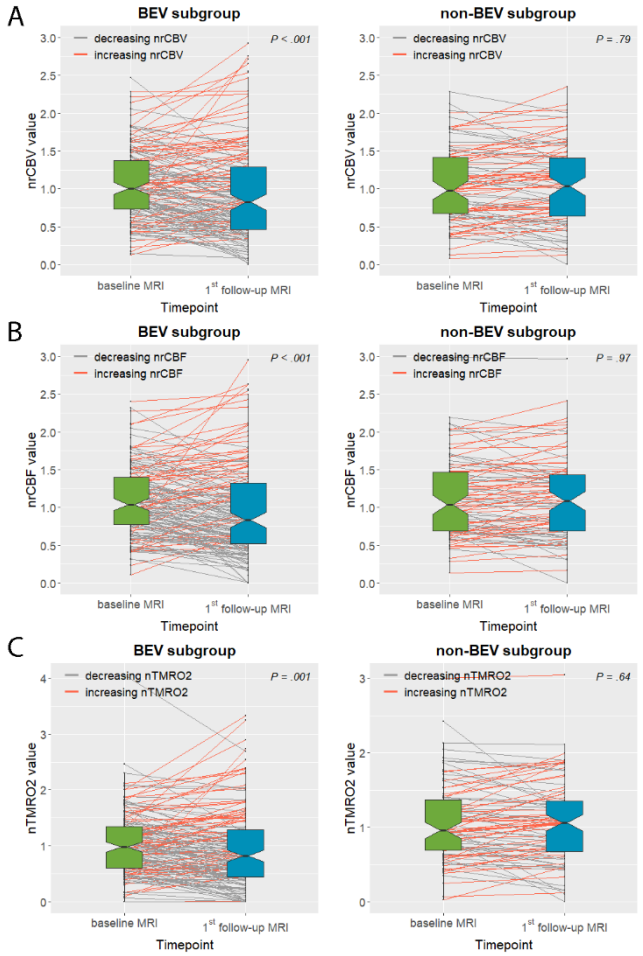
Longitudinal characterization of intratumoral angiogenesis and oxygenation by using DSC-MRI



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Key results:

- Treatment with bevacizumab (experimental treatment arm) led to a significant decrease in tumor angiogenesis and oxygenation parameters (median change of -16% for CBV (p<0.001), -18% for CBF (p<0.001) and -18% for TMRO2 (p<0.001)
- Treatment without bevacizumab (control treatment arm with lomustine chemotherapy) did not lead to a significant change in tumor angiogenesis and oxygenation parameters (median change of +1% for CBV (p=0.79), +1% for CBF (p=0.97) and 0% for TMRO2 (p=0.64)

Anti-aniogenic treatment with bevacizumab selectively decreases intratumor angiogenesis and oxygenation, thereaby reflecting its effectiveness for extending progression-free survival

Longitudinal characterization of intratumoral angiogenesis and oxygenation by using DSC-MRI

Timepoint	Parameter	HR (95% CI)	P value (FDR-adjusted)
Baseline MRI	nrCBV	0.80 (0.49, 1.29)	.59
	nrCBF	0.77 (0.46, 1.28)	.59
	nTMRO2	0.72 (0.45, 1.16)	.58
	CET (cm^3)	1.01 (0.99, 1.02)	.59
	NE (cm^3)	1.00 (1.00, 1.01)	.95
Change between baseline and first follow-up MRI	nrCBV	1.08 (0.40, 2.91)	.95
	nrCBF	0.87 (0.30, 2.49)	.95
	nTMRO2	1.03 (0.42, 2.50)	.95
	CET (cm^3)	0.96 (0.94, 0.98)	.011*
	NE (cm^3)	0.99 (0.99, 1.00)	.18

** Significant p-value for CET indicates only a predictive association for the control treatment arm, since HR<1*

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Key results:

- Cox Proportional Hazards Regression modeling was used to assess the interaction between the extracted imaging parameters (intratumoral angiogenesis, oxygenation, tumor volumes) and the effect of bevacizumab treatment on overall survival

- No predictive association in terms of overall survival was identified between any of the extracted imaging parameters and the effect of bevacizumab treatment

Conclusions

- Implementation of advanced MRI within a large multicenter phase II/III-trial is feasible and allows in-depth analysis beyond anatomical MRI to better understand the effects of novel treatment concepts in glioblastoma
- Anti-angiogenic treatment with bevacizumab (in contrast to lomustine chemotherapy) leads to a significant reduction in tumor volumes, angiogenesis and oxygenation
- Contrary to previous (uncontrolled) retrospective studies, we demonstrate that these parameters do not sufficiently explain sensitivity to bevacizumab treatment and overall survival benefit

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Further reading

Kickingereder et al. Radiology 2020

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ORIGINAL RESEARCH • NEURORADIOLOGY

Noninvasive Characterization of Tumor Angiogenesis and Oxygenation in Bevacizumab-treated Recurrent Glioblastoma by Using Dynamic Susceptibility MRI: Secondary Analysis of the European Organization for Research and Treatment of Cancer 26101 Trial

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Conflicts of interest are listed at the end of this article.

See also the editorial by Dillon in this issue.

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accompanying editorial by Dillon et al. Radiology 2020

Radiology

REVIEWS AND COMMENTARY • EDITORIAL

MRI Biomarkers of Bevacizumab Therapy Correlate with Progression-Free Survival but Not Overall Survival in Recurrent Glioblastoma

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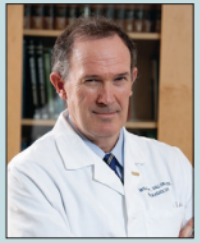
Dr Dillon is the Elizabeth A. Guillaumin professor of radiology and executive vice-chair of the Department of Radiology and Biomedical Imaging at UCSF. His research interests include head and neck radiology, brain tumor imaging, and spine pain management. He is past president of both the American Society of Neuroradiology and American Society of Head and Neck Radiology and received the Gold Medal from both organizations.



The treatment of glioblastoma currently consists of aggressive surgical resection followed by a combination of radiation therapy and the alkylating agent temozolomide. Although this is more effective than radiation or a surgical procedure alone, the median overall survival in patients with glioblastoma is still only 15 months from disease onset and the 5-year survival remains a dismal 5%. One strategy for treatment of recurrent glioblastoma has been

biomarkers that select patients who would demonstrate a sustained response to this agent.

In this issue of *Radiology*, Kickingereder et al (3) secondarily analyzed imaging data obtained in a prospective clinical trial (European Organization for Research and Treatment of Cancer, or EORTC-26101) and compared the use of bevacizumab with and without the alkylating agent lomustine for the treatment of recurrent glioblastoma. They correlated potential anatomic MRI and dynamic susceptibility contrast MRI biomarkers obtained at baseline recurrence and at first MRI follow-up with progression-free survival and overall survival. MRI-derived parametric images of whole-brain Gaussian-normalized relative cerebral blood volume (CBV), and Gaussian-normalized cerebral blood flow (CBF), and Gaussian-normalized tumor metabolic rate of oxygen consumption were processed along with volumetric segmentation of contrast-enhanced tumor and nonenhancing fluid-attenuated inversion recovery T2 volumes.

Participants treated with bevacizumab had signifi-