Journal of Neuroradiology 46 (2019) 186–192

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Original Article

Can dynamic contrast-enhanced MRI evaluate VEGF expression in brain glioma? An MRI-guided stereotactic biopsy study

Ningning Di [a,b,*], Wenna Cheng [c], Xingyue Jiang [a], Xinjiang Liu [a], Jinliang Zhou [a], Qian Xie [b], Zhihui Chu [a], Huacheng Chen [d], Bin Wang [e,**]

[a] *Department of Radiology, Binzhou Medical University Hospital, 661, Huanghe road, 256600 Binzhou, China*
[b] *Department of Radiology, Huashan Hospital Fudan University, 12, Wulumuqi road Middle, 200040 Shanghai, China*
[c] *Department of Pharmacy, Binzhou Medical University Hospital, 661, Huanghe road, 256600 Binzhou, China*
[d] *Department of Radiology, Weifang Traditional Chinese Hospital, 1055, Weizhou road, 256600 Weifang, China*
[e] *Department of Medical Imaging and Nuclear, Binzhou Medical University, 346, Guanhai road, 264000 Yantai, China*

ARTICLE INFO

Article history:
Available online 9 May 2018

Keywords:
Dynamic contrast-enhanced MRI
VEGF
Brain glioma
Biopsy

ABSTRACT

Purpose. – To investigate whether pharmacokinetic parameters derived from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) can be used to evaluate vascular endothelial growth factor (VEGF) expression in brain glioma based on a point-to-point basis.

Materials and methods. – Forty-seven patients with treatment-naïve glioma received preoperative DCE-MRI before stereotactic biopsy. We histologically quantified VEGF from section of stereotactic biopsies, and co-registered biopsy locations with localized measurements of DCE-MRI parameters including volume transfer coefficient (K^{trans}), reverse reflux rate constant (Kep), extracellular extravascular volume fraction (Ve) and blood plasma volume (Vp). The correlations between DCE-MRI parameters (K^{trans}, Kep, Ve and Vp) and VEGF were determined using Spearman correlation coefficient. $P \leq .05$ was considered statistically significant.

Results. – Seventy-nine biopsy samples were obtained and graded into 45 high-grade gliomas (HGGs) and 34 low-grade gliomas (LGGs). K^{trans} showed a significant positive correlation with VEGF expression in HGGs group ($\rho = 0.505$, $P < 0.001$) and in combined group (LGGs + HGGs) ($\rho = 0.549$, $P < 0.001$), but not in LGGs group ($P > 0.05$). Kep, Ve or Vp was not correlated with VEGF even though a positive trend showed ($P > 0.05$).

Conclusions. – DCE-MRI is a useful, non-invasive imaging technique for quantitative evaluation of VEGF, and its parameter K^{trans} other than Kep, Ve or Vp may be used as a surrogate for VEGF expression in brain gliomas.

Introduction

Angiogenesis, a hallmark of glioma, is stimulated by a number of angiogenic factors [1]. Given the complexity of a process in angiogenesis, it is remarkable that a single growth factor, vascular endothelial growth factor (VEGF), regulates this process so predominantly by inducing proliferation of vascular endothelial cells and enhancing microvascular leakage [2,3]. VEGF has been shown to correlate with biological aggressiveness, degree of malignancy and patient prognosis in gliomas, and has been as the target of current therapeutic regimens clinically [4–6].

Clinically, the method for assessment of VEGF status in glioma relies on histologic analysis using postoperative histologic analyses of biopsy samples or resected specimens. However, this process inevitably causes brain-tissue injury and prone to sampling errors and, also, the opportunity to "tailor" neoadjuvant VEGF-targeting therapy is lost. Therefore, effective clinical imaging technique settled to non-invasively predict VEGF expression in glioma is in a high priority.

Currently, dynamic contrast-enhanced MRI (DCE-MRI) is receiving much attention as a noninvasive approach for the characterization of tumors angiogenesis, given its potential in quantifying

* Corresponding author at: Department of Radiology, Binzhou Medical University Hospital, 661, Huanghe road, 256600 Binzhou, China.
** Co-corresponding author at: Department of Medical Imaging and Nuclear, Binzhou Medical University, 346, Guanhai road, 264000 Yantai, China.
E-mail addresses: dining1985@126.com (N. Di), chengwenna@126.com (W. Cheng), xyjiang188@sina.com (X. Jiang), lxj6513@163.com (X. Liu), 1315443425959@163.com (J. Zhou), xieqianjames@foxmail.com (Q. Xie), czhamj728@163.com (Z. Chu), yjtchhch@126.com (H. Chen), binwang001@aliyun.com (B. Wang).

https://doi.org/10.1016/j.neurad.2018.04.008
0150-9861/

the functional features of a target tissue perfusion and blood-brain barrier disruption in glioma by rapidly and repeatedly providing information on contrast agent exchange between the intravascular and the interstitial space [7]. The majority of clinically available DCE-MRI post-processing tools apply the extended Tofts model, which renders the following kinetic parameters: contrast volume transfer constants K^{trans} (efflux of contrast agent from vessel) and Kep (reflux to vessel), their ratio Ve, as an estimate of the extravascular-extracellular space, and the plasma volume fraction Vp [8]. This perfusion technique has proved to be reliable in optimizing glioma biopsy target [9], assessing glioma grade and differential diagnosis [10–14], predicting patient prognosis [15], and monitoring antiangiogenic therapy [16,17].

Although great efforts have been made to investigate the potential of DCE-MRI in assessing VEGF expression in glioma [18,19], precautions were not taken in these studies to ensure that the DCE-MRI measurements and glioma pathology assessments were made in matched areas, which leaves their conclusions open to question. Thus, whether DCE-MRI can serve as a reliable measure of VEGF in glioma remains poorly understood. Thereby, the aim of this study was to investigate whether DCE perfusion parameters (K^{trans}, Kep, Ve and Vp) can be used to precisely evaluate the VEGF expression in glioma by matching the perfusion parameters measurement locations with glioma biopsy targets, which was based on "point-to-point" stereotactic biopsy.

Materials and methods

Patients: from 10 May 2015 to 30 December 2016, consecutive navigated MRI-guided stereotactic biopsies of gliomas were undertaken in our hospital. Patients of either sex aged $\geq$ 18 years with a preoperative diagnosis of brain gliomas were eligible for study inclusion. Patients with metal implants that could interfere with MRI of the head were excluded from the study.

This study was approved by the local institutional review board.

MRI protocol

MRI was done using a 3.0-T MR scanner (Discovery MR750; GE Medical Systems, Milwaukee, WI, USA) equipped with an 8-channel phased-array head coil. DCE-MRI dynamic scan was acquired using 3D T1-weighted Fast Spoiled Gradient Echo sequence and setting the following sequence parameters: TR 4.6 ms; TE 1.7 ms; slice thickness 4 mm; FOV 24 cm; matrix 192 × 192; two flip angles (5°, 15°) for obtaining voxel-wise tissue longitudinal relaxation time. These sequences were aimed at converting MR intensity to the contrast agent concentration of DCE-MRI data. Then the DCE-T1 sequence was examined every 4.9 s as a phase for 60 repetitions with a total scan time of 294 s, employing the same parameters above and a 12° flip angle. The contrast agent Gd-DTPA (Omniscan, GE Healthcare, Ireland) was injected at the fifth phase of the DCE-T1 sequence with a dose of 0.1 mmol/kg of body weight and rate of 3 ml/s using a power injector via an intravenous catheter placed in the left or right antecubital vein and followed by a 20-mL saline (0.9%) flush. Matching post-contrast 3-dimensional T1-weighted (3D T1C+) (TR 7.5 ms; TE3.5 ms; FA 12°; FOV 256 × 256 × 240 mm; voxel size 1 mm; slices 170; scan time 4 min 40 s), T2-weighted FLAIR (TR 4.8 s; TE 279 s; FOV 256 × 256 × 240 mm; voxel size 4 mm; scan time 2 min 36 s), and MRS with PRESS (TR 2000 ms, TE1 32 ms, TE2 65 ms, voxel size 2 × 2 × 2 cm, 128 repetitions, FOV 256 × 256 × 240 mm, scan time 4 min 25 s).

"Point-to-point" stereotactic biopsy

Biopsy targets preset

Anatomic images obtained from 3D T1C+ were transferred to a Mei De medical workstation (SINORAO; Shenzhen, China). Biopsy targeting regions of interest (ROIs) were decided by consensus between radiologists and neurosurgeons with attention to enhancement regions or high Cho/NAA on HGGs or LGGs, and were framed (dimension (in mm) = 10 × 10 × 10) on the anatomic images *(arrows)* (Figs. 1a and 2a). The corresponding coordinate of each ROI was recorded.

Navigated MRI-guided biopsy

The anatomic images labeled with frame-based ROIs were sent to the workstation of a neuro-navigation system (StealthStation TREON; Medtronic, Minneapolis, MN, USA). All biopsy specimens were collected with frame-based stereotactic biopsies using an integrated navigation system (StealthStation i7; Medtronic). A ferromagnetic, passively navigated, 2.2 × 9 mm side-cut biopsy needle (Medtronic) was used to obtain samples within targeted ROIs (Figs. 1b and 2b). Each biopsy sample had an estimated volume of > 30 mm^3.

Imaging analyses

DCE data were processed using commercial package for DCE-MRI analysis GenIQ version installed on GE ADW4.6 workstation (GE Healthcare, Milwaukee, WI). Extended Tofts linear model (two compartments model) was used and perfusion parameters (K^{trans}, Kep, Ve and Vp) were obtained. Based on preplanned coordinates of biopsy target, ROIs were located first on post-contrast 3D T1C+ manually, and co-registered on DCE perfusion parameters map (*arrows*) (Figs. 1c and 2c). ROIs were framed with square areas of size 90–121 mm^2, and each was drawn thrice at 2-week intervals on the DCE kinetic parameters maps. To minimize error, intraclass correlation coefficient (ICC) was evaluated by correlating the mean values of the final two ROIs with the first measurement. Measurements were applied if the ICC was > 0.75. The mean of three values was used to determine the K^{trans}, Kep, Ve and Vp.

Histopathologic analysis

Each biopsy sample was fixed in 10% formalin and was blocked in paraffin and sectioned into specimens (thickness, 4 μm) for histopathologic analyses. All biopsy specimens were examined using a light microscope by a very experienced (15 years) neuropathologist blinded to the imaging results. The sections were de-waxed in xylene, dehydrated through graded alcohol concentration, and washed in tris buffer (pH 7.2). For antigen retrieval, the sections were immersed in citrate buffer (pH 6.2) at 90 °C for 1 h using a water bath and then incubated with 3% hydrogen peroxide in methanol for 15 min to block endogenous peroxidase activity. After washing twice in tris buffer, sections were incubated for 2–3 h at room temperature. Tissue blocks from each biopsy specimen were stained for polyclonal antibody against human VEGF (Santa Cruz Biotechnology, Santa Cruz, CA, USA) at a dilution range of 1:100. As described in a previous study [19], the percentage of immunoreactive positive cells was scored to quantitate VEGF expression (Figs. 1d and 2d). Mean percentage of VEGF-positive cells was determined by sections in three representative fields of concentrated tumor cells at a magnification of ×200.

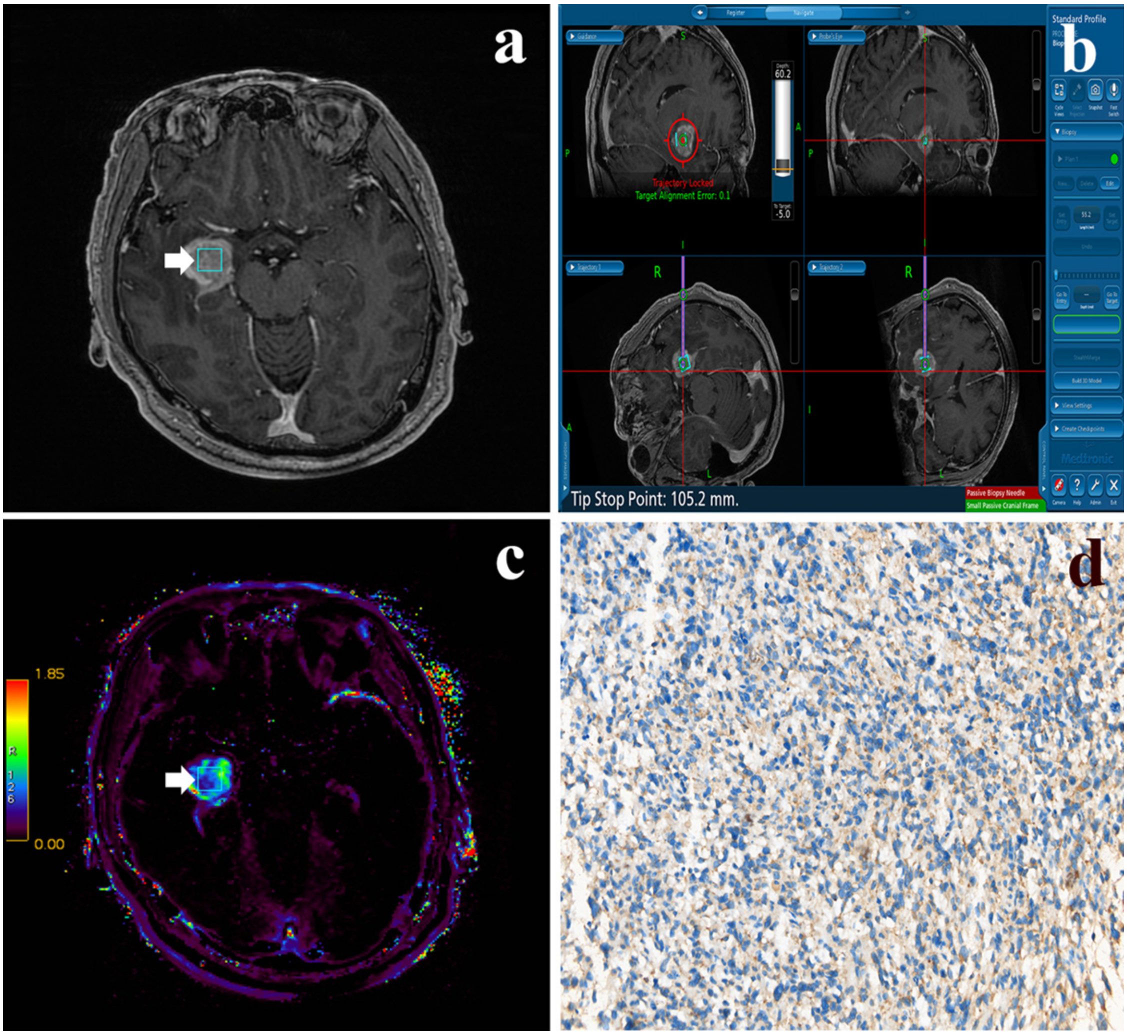

Fig. 1. A 61-year-old male patient with anaplastic astrocytoma located in right temporal lobe. One ROI was pre-established on hyper-enhancement and defined as biopsy target from 3D T1C+ (*arrow*) (a). Biopsy specimen within ROI was obtained with biopsy needle guided by neuro-navigation system (b). The co-registered ROI on K^{trans} parametric map was featured with high K^{trans} (*arrow*) (c), and the corresponding biopsy specimen shows high VEGF expression (d).

Statistical analyses

Statistical analyses were carried out using SPSS v20.0 (IBM, Armonk, NY, USA). The Spearman test was used to calculate correlation coefficients between the DCE perfusion parameters (K^{trans}, Kep, Ve and Vp) and corresponding VEGF expression. $P \leq 0.05$ was considered significant.

Results

Forty-seven patients with treatment-naïve glioma were enrolled in our study. Among them, 3 patients were excluded because of significant susceptibility artifacts induced by movement. A further 4 patients were excluded because of poor co-registration and poor localization of the biopsy site during surgery. Finally, 79 biopsy samples from 40 subjects were recruited and graded according to the World Health Organization Classification of Tumors of the Central Nervous System (2016) [20]. Finally, 45 biopsy samples with high-grade glioma (HGG) (30 anaplastic astrocytomas grade III, 15 glioblastomas grade IV) and 34 biopsy samples with low-grade glioma (LGG) (diffuse astrocytoma grade II) were included in the analysis.

Mean registration error for these 40 subjects was 1.52 ± 0.21 mm. The target area (range, 90–121 mm^2) was dependent upon manual operation and the co-registration error was maintained at < 0.6 mm. Mean error among the three measurements for the target area was 3.05 ± 1.62 mm^2. The ICC was > 0.75 for DCE-derived K^{trans} measurements.

DCE-derived K^{trans} showed a significant positive correlation with VEGF expression in HGGs ($\rho = 0.505$, $P < 0.001$) and combined group (HGGs + LGGs) ($\rho = 0.549$, $P < 0.001$). However, when compared Kep, Ve, or Vp with VEGF, there was no significant correlation ($P > 0.05$). (Table 1, Figs. 3 and 4).

Discussion

Perfusion MRIs, including dynamic susceptibility-contrast (DSC)-MRI with T2* weighted echo planar sequence and dynamic contrast-enhanced (DCE)-MRI with T1-weighted two/three-dimensional fast gradient echo sequence can be applied to measure tissues perfusion noninvasively and repeatedly in vivo [21,22]. Compared to DSC-MRI, DCE-MRI offers the advances of less sensitivity to susceptibility artifacts, better quantification of microvascular permeability, and more quantitative results [23]. Although this technique is becoming widely applied clinically, the conclusion that whether DCE-derived parameters can be as markers for VEGF expression in tumor remains poorly understood. Some studies confirmed the potential of DCE perfusion parameters

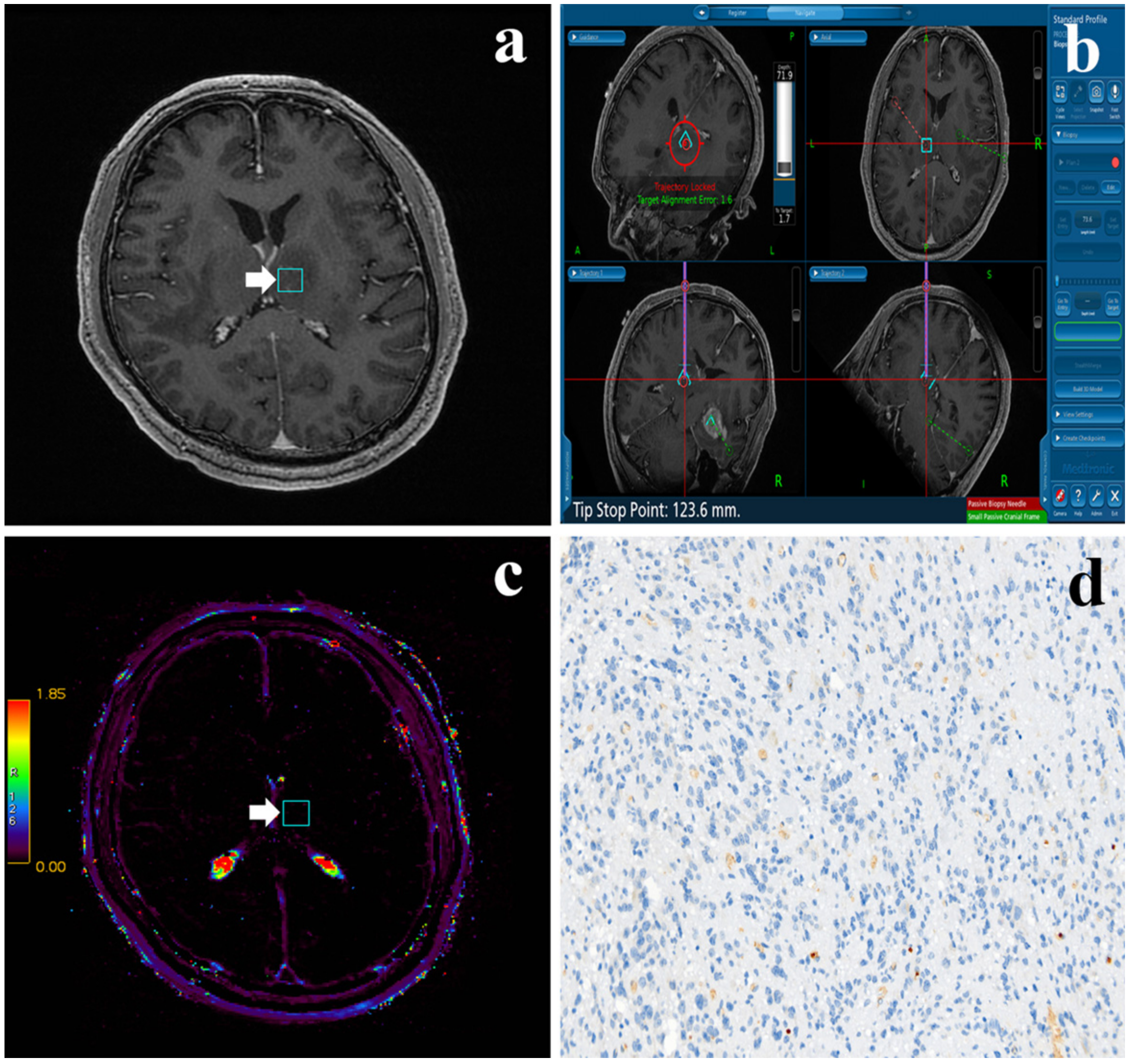

Fig. 2. Another biopsy target with diffuse astrocytoma from the same patient was located in left thalamus. The ROI was pre-established on axial 3D T1C+ image and defined as biopsy target (*arrow*) (a). Biopsy specimen within ROI was obtained with biopsy needle guided by neuro-navigation system (b). The co-registered ROI on K^{trans} parametric map was featured with low K^{trans} (*arrow*) (c), and the corresponding biopsy specimen shows low VEGF expression (d).

Table 1
Correlations between parametric values and VEGF expression in HGGs, LGGs and combined group (LGGs + HGGs).

	HGGs		LGGs		LGGs + HGGs	
	ρ	P	ρ	P	ρ	P
K^{trans}	0.505[a]	< 0.001	−0.171	0.34	0.549[a]	< 0.001
Kep	0.298	0.072	0.330	0.075	0.216	0.068
Ve	0.286	0.157	0.209	0.313	0.22	0.091
Vp	0.309	0.062	0.34	0.259	0.398	0.081

[a] Correlation was significant at 0.05 (two-tailed).

in predicting VEGF expression status in tumors [24,25]; however, others reported conflict results [18,19]. These conflict results may be due to the failure to match DCE-MRI measurements map with the pathology samples obtained by radical resection, partial resection, or stereotactic biopsy. Some studies have shown that such failure to have matching regions on both imaging and histopathology can influence the correlation between them [26,27]. Goh et al. [26] found positive correlation between the perfusion parameters and angiogenesis markers when they did not match locations, but this correlation disappeared after matching was done [27].

Thereby, the mismatch on DCE-MRI measurement and pathology assessment always limits the effectiveness of DCE perfusion parameters in evaluating VEGF expression in glioma owning to spatial heterogeneity in tumors [28]. To overcome the disadvantage, "point-to-point" stereotactic biopsy was introduced in our study, to the best of our knowledge, which is the best method presently available method to match regions on both imaging and histopathology for brain tumors [29,30]. To achieve this, first, ROIs of 10 × 10 mm were preset on the 3D T1+ as the biopsy sites, and the corresponding coordinates were obtained. Then, anatomic images with ROIs were transferred to the workstation of the neuronavigation system; and biopsy specimens from the preplanned ROIs were obtained by neurosurgeon using a ferromagnetic, passively navigated, 2.2 × 9-mm side-cut biopsy needle. Finally, ROIs from anatomic images were

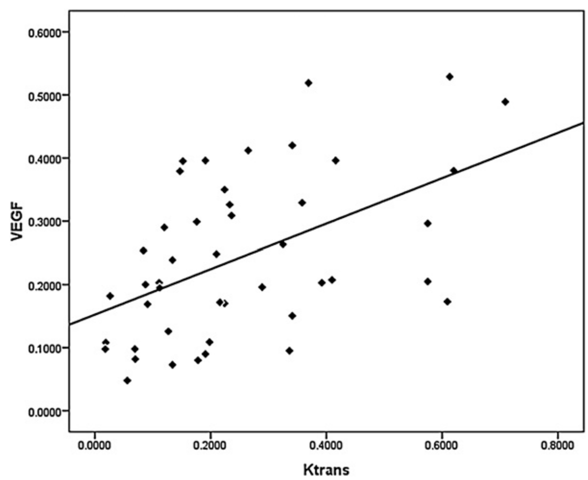

Fig. 3. Scatterplot showed significant correlation between K^{trans} and VEGF expression in HGGs group ($\rho = 0.505$, $P < 0.001$).

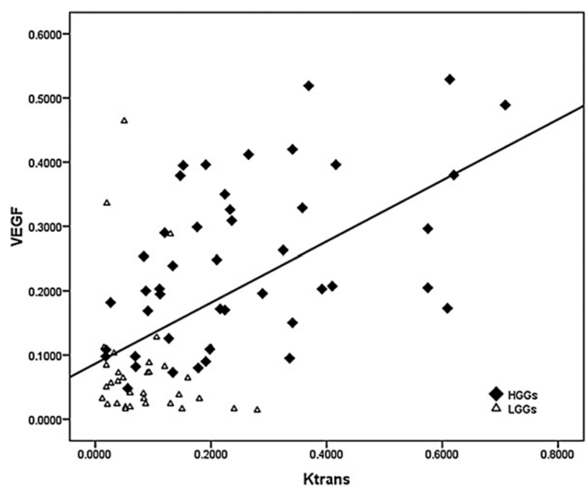

Fig. 4. Scatterplot showed significant correlation between K^{trans} and VEGF expression in combined group (HGGs + LGGs) ($\rho = 0.549$, $P < 0.001$).

reregistered to the DCE-MRI measurements, and the correlation between the perfusion parameters (K^{trans}, Kep, Vp, and Ve) and the VEGF expression of the biopsy samples was analyzed.

In addition, attention was paid to three other points with regard to the location of ROIs and measurement of DCE MRI kinetic parameters. First, the error in matching the centric coordinates of the biopsy target with the centric coordinates of the manually drawn ROIs for DCE-MRI parameters measurements was restricted to no more than 0.6 mm. Second, the mean fiducial error caused by the discrepancy between the location in the neuronavigational image and that in the anatomic image was controlled to be no more than 2 mm, which was deemed a good registration clinically. Last, each ROI of DCE-MRI parameters measurement was drawn thrice, with the same area as the anatomic images, to ensure that the mean area error among them was $3.05 \pm 1.62\ mm^2$ and the ICC was > 75%; this guaranteed that the DCE-MRI parameters measurements had good repeatability and accuracy.

By comparing histologic changes on image-guided biopsies with image-based measures of perfusion, we confirmed the obvious positive correlation between the K^{trans} and VEGF in the group of high-grade glioma, as in the previous study [31], and also confirmed this correlation in the combined group (including high-grade glioma and low-grade glioma). This result suggested DCE-derived K^{trans} can be a reliable surrogate for evaluating VEGF expression in gliomas. K^{trans} is defined as the volume transfer constant between plasma and interstitial space, and depends on both the leakiness of the vessels and the total surface of leaky capillaries in brain tumors, thereby; high K^{trans} measurement in a voxel may be due to very leaky vessels, many leaky capillaries within the voxel, or a combination of both [8,32]. VEGF, as a predominant factor in angiogenesis, not only enhances microvascular leakage but also stimulates mitosis of endothelial cells to develop a new vascular infrastructure that increases leaky microvascular [2,3]. Thereby, it is reasonable DCE-derived K^{trans} can assess tumor hemodynamic changes induced by VEGF expression in our study, which is corresponding to the finding that K^{trans} was decreased when VEGF signaling was blocked [16,17], and is supported by the previous investigations by Zhang et al., and Ma et al. [24,25]. However, such positive correlation between K^{trans} and VEGF expression in gliomas was not demonstrated from the studies conducted by Awasthi et al. and Haris et al. [18,19]. These conflict results may be attributed to the lack of stereotactic image-matched histologic specimens, and the correlation between the histology and the DCE-MRI measurements at a local level cannot be reached. Remarkably, the advantage of this study was that the diligence in matching of biopsy sites and imaged sites with attention to glioma heterogeneity and spatial correlation.

Vp is another important DCE-MRI kinetic parameter and is defined as the blood Vp per unit volume of tissue. This parameter has been as a noninvasive imaging biomarker for preoperative grading of astrocytoma and differentiating brain tumors [10,11]. Given its advantages of lower sensitivity to susceptibility artifacts and its ability to provide additional information regarding tissue permeability compared with DSC-derived rCBV, this parameter has been recommended as an alternative imaging biomarker for the assessment of blood volume [33]. VEGF is supposed to determine the tumor blood volume, and may be related with Vp values. Thereby, our result compared Vp with VEGF in the groups with low-grade glioma, high-grade glioma and the combined glioma respectively. Despite these efforts we could not find a significant correlation between Vp and VEGF ($P > 0.05$), although a positive trend was confirmed. This result was in accordance in a previous study based on "point-to-point biopsy", where the authors found the CT perfusion derived CBV was not correlated with VEGF in glioma [34]. The failure of the significant correlation between Vp and VEGF may be explained by the fact that high vascular permeability induced by VEGF can result in a high interstitial pressure in tumor, which may make microvasculature distort, collapse, and even divert [35]. This will reduce the effective blood flow and limit the volume of contrast agent distribution. Thus, the using DCE-derived Vp in evaluating VEGF expression in glioma may not be appropriate from our study.

Interestingly, based on point-to-point biopsy guided by stereotactic MRI, Jensen RL, et al. demonstrated a positive correlation between VEGF with Vp but not with K^{trans} [36], which was contradictory to the result showed in our study. Two possible explanations can be applied as following. Firstly, the sample size was small ($n = 18$) in the above-mentioned study. Jain KK, et al. demonstrated a positive correlation between the MRI perfusion parameters and pathology in the group with large sample size, but this positive correlation disappeared when the sample divided into two groups with smaller sample size [37]. In the current study, 79 samples were included, of which 34 with low-grade glioma and 45 with high-grade glioma at histopathology. Thereby, the correlation between DCE-MRI parameters and VEGF may be less biased by sample size. Secondly, this might to be related to the meningioma enrolled in the study conducted by Jensen RL et al. In therapy, VEGF play an important role in tumor vascularity, which will affect the permeability or the perfusion of tumor. However, Lamszus et al. could not find a relationship between VEGF and vascularity in meningioma [38], thereby, it was not surprised that the DCE-MRI kinetic parameters were independent from VEGF expression in meningioma [39]. Moreover, contrary to the primary brain glioma, meningioma is mesenchymal origin and lacks permeability barrier structure such as endothelial tight junction, which is regulated by VEGF [40]. Thereby, the potential of DCE-MRI in evaluating VEGF expression may be varied from meningioma, glioma, or combined the two brain tumors, and our study only focusing on the glioma may help better understand the potential of DCE-MRI kinetic parameters in evaluating VEGF expression in glioma.

Gliomas have complex and heterogeneous tumor vasculartture; thus, different regions within a tumor may show different grades, aggressiveness, and treatment response based on heterogeneity of tumor angiogenesis. Biopsy is a vital way to evaluate the malignance of glioma; however, diagnostic errors may result from heterogeneity of gliomas. Thereby, identifying the regions with more aggressive angiogenic tumor tissue is essential for adequate evaluation of the glioma malignancy. Owning to the positive correlation between K^{trans} and VEGF of the stereotactic biopsy, it is reasonable to hypothesize that K^{trans}-based biopsy target provides significant information on glioma malignancy. Thus, qualitative evaluation of the DCE-derived K^{trans} map may add value to multi-parametric MR imaging (such as MR spectroscopy, apparent diffusion coefficient, and DSC) and PET for optimizing glioma biopsy. Clinically, antiangiogenic treatment with bevacizumab (anti-VEGF monoclonal antibody) has been a major research focus in patients with newly diagnosed malignant gliomas. Thereby, our result may also provide more information on the optimizing glioma anti-VEGF therapy.

However, the present study had three main limitations. First, in studies involving image-guided biopsy specimens, the major problem is correct matching of imaged areas and surgical biopsy sites. We used a surgical navigation system and MRI for biopsy guidance and then matched the biopsy site with DCE-derived K^{trans} maps as diligently as possible. To minimize error, we excluded 7 patients, mainly due to poor co-registration or poor localization of the biopsy site during surgery. Placement of a ROI that matched the biopsy site by manual operation was the second limitation, although three radiologists determined the drawing of ROIs independently. Finally, studies consist of larger samples will be needed in future studies to test our results.

In summary, based on the point-to-point basis by using coregistered MRI and stereotactic biopsies, this study confirmed the potential of DCE-derived K^{trans} as a surrogate for evaluation for VEGF in brain glioma. This might help improve DCE-MRI in optimizing the biopsy targeting and anti-angiogenesis treatment for glioma.

Author contributions

N.D. and B.W. conceived and designed research. N.D., W.C. and X.J. conducted experiments. X.L., J.Z., H.C., Z.C. and Q.X. contributed new reagents and/or analytical tools. N.D. and W.C. analyzed data. ND wrote the manuscript. B.W., W.C. and X.J. revised the manuscript. All authors read and approved the manuscript. Besides,this work was supported by National Natural Science Foundation of China (Grant No.81171303) and the Scientific Research Foundation of Binzhou Medical University(Grant No.BY2017KYQD13).

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Fischer I, Gagner JP, Law M, Newcomb EW, Zagzag D. Angiogenesis in gliomas: biology and molecular pathophysiology. Brain Pathol 2005;15:297–310.
[2] Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. Nature 2011;473:298–307.
[3] Weis SM, Cheresh DA. Pathophysiological consequences of VEGF-induced vascular permeability. Nature 2005;437:497–504.
[4] Machein MR, Plate KH. VEGF in brain tumors. J Neurooncol 2000;50:109–20.
[5] Korkolopoulou P, Patsouris E, Konstantinidou AE, Pavlopoulos PM, Kavantzas N, Boviatsis E, et al. Hypoxia-inducible factor 1alpha/vascular endothelial growth factor axis in astrocytomas. Associations with microvessel morphometry, proliferation and prognosis. Neuropathol Appl Neurobiol 2004;30: 267–78.
[6] Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370:699–708.
[7] Tofts PS, Kermode AG. Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1 Fundamental concepts. Magn Reson Med 1991;17:357–67.
[8] Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, et al. Estimating kinetic parameters from dynamic contrast-enhanced T (1)-weighted MRI of a diffusible tracer: standardized quantities and symbols. J Magn Reson Imaging 1999;10:223–32.
[9] Keil VC, Pintea B, Gielen GH, Greschus S, Fimmers R, Gieseke J, et al. Biopsy targeting with dynamic contrast-enhanced versus standard neuronavigation MRI in glioma: a prospective double-blinded evaluation of selection benefits. J Neurooncol 2017;133:155–63.
[10] Nguyen TB, Cron GO, Perdrizet K, Bezzina K, Torres CH, Chakraborty S, et al. Comparison of the diagnostic accuracy of DSC- and dynamic contrast-enhanced MRI in the preoperative grading of astrocytomas. AJNR Am J Neuroradiol 2015;36:2017–22.
[11] Arevalo-Perez J, Kebede AA, Peck KK, Diamond E, Holodny AI, Rosenblum M, et al. Dynamic contrast-enhanced MRI in low-grade versus anaplastic oligodendrogliomas. J Neuroimaging 2017;26:366–71.
[12] Yun TJ, Park CK, Kim TM, Lee SH, Kim JH, Sohn CH, et al. Glioblastoma treated with concurrent radiation therapy and temozolomide chemotherapy: differentiation of true progression from pseudoprogression with quantitative dynamic contrast-enhanced MR imaging. Radiology 2015;274:830–40.
[13] Hussain NS, Moisi MD, Keogh B, McCullough BJ, Rostad S, Newell D, et al. Dynamic susceptibility contrast and dynamic contrast-enhanced MRI characteristics to distinguish microcystic meningiomas from traditional Grade I meningiomas and high-grade gliomas. J Neurosurg 2017;126:1220–6.
[14] Lu S, Gao Q, Yu J, Li Y, Cao P, Shi H, et al. Utility of dynamic contrast-enhanced magnetic resonance imaging for differentiating glioblastoma, primary central nervous system lymphoma and brain metastatic tumor. Eur J Radiol 2016;85:1722–7.
[15] Nguyen TB, Cron GO, Mercier JF, Foottit C, Torres CH, Chakraborty S, et al. Preoperative prognostic value of dynamic contrast-enhanced MRI-derived contrast transfer coefficient and plasma volume in patients with cerebral gliomas. AJNR Am J Neuroradiol 2015;36:63–9.
[16] Piludu F, Marzi S, Pace A, Villani V, Fabi A, Carapella CM, et al. Early biomarkers from dynamic contrast-enhanced magnetic resonance imaging to predict the response to antiangiogenic therapy in high-grade gliomas. Neuroradiology 2015;57:1269–80.
[17] O'Neill AF, Qin L, Wen PY, de Groot JF, Van den Abbeele AD, Yap JT. Demonstration of DCE-MRI as an early pharmacodynamic biomarker of response to VEGF Trap in glioblastoma. J Neurooncol 2016;130:495–503.
[18] Haris M, Husain N, Singh A, Husain M, Srivastava S, Srivastava C, et al. Dynamic contrast-enhanced derived cerebral blood volume correlates better with leak correction than with no correction for vascular endothelial growth factor, microvascular density, and grading of astrocytoma. J Comput Assist Tomogr 2008;32:955–65.
[19] Awasthi R, Rathore RK, Soni P, Sahoo P, Awasthi A, Husain N, et al. Discriminant analysis to classify glioma grading using dynamic contrast-enhanced MRI and immunohistochemical markers. Neuroradiology 2012;54:205–13.
[20] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131:803–20.
[21] Viallon M, Cuvinciuc V, Delattre B, Merlini L, Barnaure-Nachbar I, Toso-Patel S, et al. State-of-the-art MRI techniques in neuroradiology: principles, pitfalls, and clinical applications. Neuroradiology 2015;57:441–67.
[22] Dujardin MI, Sourbron SP, Chaskis C, Verellen D, Stadnik T, de Mey J, et al. Quantification of cerebral tumour blood flow and permeability with T1-weighted dynamic contrast enhanced MRI: a feasibility study. J Neuroradiol 2012;39(4):227–35.
[23] Yeo DM, Oh SN, Jung CK, Lee MA, Oh ST, Rha SE, et al. Correlation of dynamic contrast-enhanced MRI perfusion parameters with angiogenesis and biologic aggressiveness of rectal cancer: preliminary results. J Magn Reson Imaging 2013;41:474–80.
[24] Zhang XM, Yu D, Zhang HL, Dai Y, Bi D, Liu Z, et al. 3D dynamic contrast-enhanced MRI of rectal carcinoma at 3 T: correlation with microvascular density and vascular endothelial growth factor markers of tumor angiogenesis. J Magn Reson Imaging 2008;27:1309–16.
[25] Ma L, Xu X, Zhang M, Zheng S, Zhang B, Zhang W, et al. Dynamic contrast-enhanced MRI of gastric cancer: correlations of the pharmacokinetic

parameters with histological type, Lauren classification, and angiogenesis. Magn Reson Imaging 2017;37:27–32.
[26] Goh V, Halligan S, Daley F, Wellsted DM, Guenther T, Bartram CI. Colorectal tumor vascularity: quantitative assessment with multidetector CT—do tumor perfusion measurements reflect angiogenesis? Radiology 2008;249: 510–7.
[27] Dighe S, Blake H, Jeyadevan N, Castellano I, Koh DM, Orton M, et al. Perfusion CT vascular parameters do not correlate with immunohistochemically derived microvessel density count in colorectal tumors. Radiology 2013;268:400–10.
[28] Meacham CE, Morrison SJ. Tumour heterogeneity and cancer cell plasticity. Nature 2013;501:328–37.
[29] Barajas RF, Hodgson JG, Chang JS, Vandenberg SR, Yeh RF, Parsa AT, et al. Glioblastoma multiforme regional genetic and cellular expression patterns: influence on anatomic and physiologic MR imaging. Radiology 2010;254:564–76.
[30] Christoforidis GA, Yang M, Abduljalil A, Chaudhury AR, Newton HB, McGregor JM, et al. "Tumoral pseudoblush" identified within gliomas at high-spatial-resolution ultrahigh-field-strength gradient-echo MR imaging corresponds to microvascularity at stereotactic biopsy. Radiology 2012;264: 210–7.
[31] Ningning D, Chenjun Y, Wenna C, et al. Correlation of dynamic contrast-enhanced MRI derived volume transfer constant with histological angiogenic markers in high grade gliomas. J Med Imaging Radiat Oncol 2018, http://dx.doi.org/10.1111/1754-9485.12701 [Epub ahead of print].
[32] Alcaide-Leon P, Pareto D, Martinez-Saez E, Auger C, Bharatha A, Rovira A. Pixel-by-pixel comparison of volume transfer constant and estimates of cerebral blood volume from dynamic contrast-enhanced and dynamic susceptibility contrast-enhanced MR imaging in high-grade gliomas. AJNR Am J Neuroradiol 2015;36:871–6.
[33] Artzi M, Liberman G, Nadav G, Vitinshtein F, Blumenthal DT, Bokstein F, et al. Human cerebral blood volume measurements using dynamic contrast enhancement in comparison to dynamic susceptibility contrast MRI. Neuroradiology 2015;57:671–8.
[34] Jain R, Gutierrez J, Narang J, Scarpace L, Schultz LR, Lemke N, et al. In vivo correlation of tumor blood volume and permeability with histologic and molecular angiogenic markers in gliomas. AJNR Am J Neuroradiol 2011;32:388–94.
[35] DeVries AF, Kremser C, Hein PA, Griebel J, Krezcy A, Ofner D, et al. Tumor microcirculation and diffusion predict therapy outcome for primary rectal carcinoma. Int J Radiat Oncol Biol Phys 2003;56:958–65.
[36] Jensen RL, Mumert ML, Gillespie DL, Kinney AY, Schabel MC, Salzman KL, et al. Preoperative dynamic contrast-enhanced MRI correlates with molecular markers of hypoxia and vascularity in specific areas of intratumoral microenvironment and is predictive of patient outcome. Neuro Oncol 2014;16:280–91.
[37] Jain KK, Sahoo P, Tyagi R, Mehta A, Patir R, Vaishya S, et al. Prospective glioma grading using single-dose dynamic contrast-enhanced perfusion MRI. Clin Radiol 2015;70:1128–35.
[38] Lamszuz K, Lengler U, Schmidt NO, Stavrou D, Ergün S, Westphal M, et al. Vascular endothelial growth factor, hepatocyte growth factor/scatter factor, basic fibroblast growth factor, and placenta growth factor in human meningiomas and their relation to angiogenesis and malignancy. Neurosurgery 2000;46:938–47.
[39] Keil VC, Pintea B, Gielen GH, Hittatiya K, Datsi A, Simon M, et al. Meningioma assessment: Kinetic parameters in dynamic contrast-enhanced MRI appear independent from microvascular anatomy and VEGF expression. J Neuroradiol 2018, http://dx.doi.org/10.1016/j.neurad.2018.01.050 [Epub ahead of print].
[40] Argaw AT, Asp L, Zhang J, Navrazhina K, Pham T, Mariani JN, et al. Astrocyte-derived VEGF-A drives blood-brain barrier disruption in CNS inflammatory disease. J Clin Invest 2012;122:2454–68.