Inverse Perfusion Requirements of Supra- and Infratentorial Brain Metastases Formation

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Background and Aims: Vascular border zones and the gray-white matter junction are preferred sites for the development of brain metastases (BM), whereas microvascular lesions are known to be a protective factor. In this proof of concept study, we aim to study the relationship of blood perfusion and the spatial distribution of BM.

Materials and Methods: An average CT perfusion atlas of 107 healthy patients was created. Voxel-wise reference perfusion values were extracted from BM-negative and BM-positive regions in a second cohort of 100 untreated patients harboring 809 BM confirmed by MRI. A comparison of regional perfusion values was performed using the independent t-test.

Results: In contrast to supratentorial BM that develop preferably in areas with lower CBV/CBF and longer MTT/TTP compared to the average regional perfusion (p < 0.001), infratentorial BM showed a higher CBV/CBF and shorter MTT/TTP (p < 0.001).

Conclusion: Our results imply differing pathophysiological mechanisms underlying supra- and infratentorial BM spreading. The inverse perfusion patterns may result from differences in vascular supply, hemodynamic requirements, and/or production of pro-angiogenic factors.

Keywords: blood-brain barrier, cerebral blood flows, hemodynamics, MR tomography, multidetector computed tomography, neoplasm metastases, neoplasms, perfusion imaging

INTRODUCTION

In principal, there are two main hypotheses on the development of brain metastases (BM). The “seed and soil” hypothesis states that metastatic cells favor a particular biochemical environment or tend to colonize selectively in suitable tissues (soils) due to cell surface and endothelium properties (1, 2). Furthermore, the “anatomical-mechanical” theory proposes that dissemination of metastases follows arterial vessel caliber and local blood flow (3).

Prior studies already demonstrated that the presence and the amount of small vessel ischemic disease are protective factors against the development of BM (4–7). Hwang et al. found a
higher propensity of BM in vascular border zones and the gray-white matter junction (8). These findings suggest a relevant impact of brain perfusion on BM formation.

Here, we aim to study the relationship of the spatial distribution of the BM of 100 untreated patients and the underlying blood perfusion pattern. We hypothesize that all BM would preferably develop in areas where physiological perfusion is rather high compared to areas without any BM. We further hypothesize that central necrotic BM tend to colonize in areas with less perfusion.

MATERIALS AND METHODS

This single center, retrospective study was conducted in compliance with the local ethics committee (Ethik-Kommission der Aerztekammer Hamburg, WF-018/15) with a waiver of informed consent.

CT Perfusion Atlas

Cerebral blood flow in cancer patients has been shown to be altered due to paraneoplastic changes, chemotherapy administration, neoangiogenesis, and/or disruption of the blood-brain barrier (9, 10). Therefore, we used pooled whole-brain CT perfusion datasets of a reference population. The perfusion atlas was generated from 107 patients who were triaged by CT perfusion for symptoms of transient ischemic attack but without evidence of infarction or any perfusion abnormality, symptoms on follow up, or vascular abnormality that was verified by MRI 24h later (11). Quantitative perfusion maps were obtained for cerebral blood volume (CBV in ml/100 g brain tissue), cerebral blood flow (CBF in ml/100 g brain tissue/min), mean transit time (MTT in s), and time to peak (TTP in s). CT perfusion was performed on a Somatom Flash scanner (Siemens Healthcare, Erlangen, Germany) by applying the following scan parameters: 80 kV, 200 mAs, collimation 2 x 64 x 0.6 mm, 5 mm slice.
reconstruction, 1.5 s sampling rate for 45 s, biphasic i.v. injection with 30 ml of 400 mM/ml iodinated contrast medium followed by 30 ml NaCl chaser bolus with a flow rate of 4 ml/s.

All perfusion raw data were processed in a central core-lab on a workstation dedicated for perfusion analysis with motion correction and low band temporal noise removal (Syngo mmwp VE52A with VPCT-Neuro; Siemens Healthcare, Erlangen, Germany). Non-parenchymal voxels corresponding to bone, vasculature, calcification, and cerebrospinal fluid were automatically excluded by adaptive intensity thresholding. Perfusion parameter maps were calculated based on a deconvolution model by least mean squares fitting (12). Perfusion data sets with erratic or incomplete arterial and venous attenuation time curves were excluded (n = 5). All calculated perfusion maps were reformatted to 1 mm Montréal Neurological Institute (MNI) standard space using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library 5.0 (Analysis Group, Oxford, UK) with nearest neighbor interpolation so that quantitative image gray values remained unchanged (13). Mean voxel-wise perfusion parameter maps normalized to the MNI space were then used in our study cohort to obtain normal perfusion values for each voxel of the perfusion map and each voxel with a BM (Figures 1A–D).

BM atlas
Since CT does not offer sufficient tissue contrast for reliable detection of BM we decided to delineate and define BM location by contrast-enhanced MRI due to its superior resolution (14). One hundred consecutive patients with different tumor entities screened between 01/2014 and 03/2015 in our university hospital fulfilled the inclusion and exclusion criteria given in Figure 2. In particular, all patients included were not known to have BM prior to MRI and were therefore untreated for BM.

MRI protocol
The study was conducted using 1.5 Tesla MRI systems in 94 patients (Magnetom® Sonata, Siemens Healthcare, Erlangen, Germany; Magnetom® Symphony, Siemens Healthcare, Erlangen, Germany, or Magnetom® Avanto, Siemens Healthcare, Erlangen, Germany) and 3 Tesla MRI scanners in 6 patients (Magnetom+ Skyra, Siemens Healthcare, Erlangen, Germany or Ingenia, Philips Medical Systems, Best, The Netherlands).

The standard imaging protocol always included axial T1w spin echo (2D T1 SE+) with flow compensation and/or three-dimensional T1w gradient echo sequences (3D T1 GRE+) following weight-adjusted i.v. Gadolinium injection, respectively. If both sequences were acquired, axial 3D T1 GRE+ was processed for further analysis. Sequence parameters for the different MRI scanners are given in Table 1.

A necrotic BM was defined as central hypointense area surrounded by a rim of marked enhancement on post-contrast T1-weighted MR images.

Segmentation of BM
In 100 patients we detected and semi-manually segmented a total of 809 BM. Semi-automated segmentation was performed using the Analyze Software System 11.0 (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN, USA) (15). Afterwards, axial post-contrast T1-weighted MR images were automatically co-registered to the MNI 1mm brain by using the FMRIB

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**FIGURE 2** | Summary of the inclusion (Left) and exclusion criteria (Right). *No surgery, radiotherapy, or chemotherapy (e.g., bevacizumab) for treatment of BM previous to MRI.
Software Library 5.0 linear (affine) registration tool. Correct registration of all post-contrast T1-weighted MR images and the segmented BM to the MNI brain was secured through visual inspection by two readers (T. S. and S. S.). From all BM masks in MNI space, a binary sum mask was created, subdividing the MNI brain in regions with \(\text{BM}_{\text{pos}}\) and without BM \(\text{BM}_{\text{neg}}\).

**Statistical Analysis**

Statistical analysis was conducted using IBM SPSS Statistics software (IBM \(^{\text{R}}\) 2011, version 20, Armonk, New York, USA) and R (The R Foundation, version 3.3.1 Vienna, Austria). The differences in CBF, CBV, MTT, and TTP between all BM\(_{\text{pos}}\) and BM\(_{\text{neg}}\) voxels were compared by the independent \(t\)-test since we had a large enough sample size. Voxels with more than one BM were weighted according to the number of BM occurring within the voxel. Mann-Whitney \(U\)-test was performed to determine voxel-wise differences of perfusion values among BM with and without central necrosis. If not otherwise indicated, data are given as median \(\pm\) standard deviation.

**RESULTS**

**Descriptive Statistics**

Patient age at diagnosis of BM was 62 \(\pm\) 12.5 years. The number of patients, number of BM, and number of BM with central necrosis for the whole group and for the different primary tumors are described in Table 2. Primary tumor entities were lung cancer \((n = 51): 37\) non-small lung cancer and 14 small cell lung cancer, skin cancer \((n = 17): 16\) melanoma and one Merkel-cell carcinoma, breast cancer \((n = 10)\), genitourinary cancer \((n = 10): 1\) choriocarcinoma, two prostate, two kidney, three urothelial cell cancer, and two testicular cancer, cancer of unknown primary \((n = 6)\), gastrointestinal cancer \((n = 4): 2\) colon and two rectal cancer, and sarcoma \((n = 2)\).

**Perfusion Patterns**

Among all patients, CBF \((56 \pm 34\) vs. \(59 \pm 35\) ml/100 g/min, \(p < 0.001)\) and CBV \((3.7 \pm 2.0\) vs. \(3.9 \pm 2.1\) ml/100 g, \(p < 0.001)\) were lower and MTT \((4.8 \pm 0.7\) vs. \(4.7 \pm 0.7\) s, \(p < 0.01)\) and TTP

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**Table 1**

| Variable/Sequence | Magnetom\(^{\text{R}}\) Sonata | Magnetom\(^{\text{R}}\) Symphony | Magnetom\(^{\text{R}}\) Avanto | Magnetom\(^{\text{R}}\) Skyra | Ingenia |
|-------------------|-------------------------------|-------------------------------|-----------------------------|-----------------------------|---------|
| Tesla             | 1.5                           | 1.5                           | 1.5                         | 3                           | 3       |
| No. of patients   | 11                            | 25                            | 58                          | 2                           | 4       |
| 2D T1 SE\(^{+}\) |                               |                               |                             |                             |         |
| TE (ms)           | 10                            | 17                            | 12                          | 12                          | 10      |
| TR (ms)           | 460                           | 690                           | 556                         | 550.0                       | 600     |
| Flip angle        | 70°                           | 70°                           | 70°                         | 150°                        | 70°     |
| Matrix            | 192 \(\times\) 256            | 192 \(\times\) 256            | 192 \(\times\) 256          | 432 \(\times\) 512          | 432 \(\times\) 432 |
| FOV               | 172.5 \(\times\) 230          | 172.5 \(\times\) 230          | 172.5 \(\times\) 230        | 194.1 \(\times\) 230        | 230 \(\times\) 230 |
| Pixel size (mm)   | 0.9 \(\times\) 0.9            | 0.9 \(\times\) 0.9            | 0.9                         | 0.4 \(\times\) 0.4          | 0.5 \(\times\) 0.5 |
| No. of slices     | 20                            | 25                            | 25                          | 32                          | 28      |
| Slice thickness (mm) | 5                           | 5                             | 4                           | 4                           | 4       |
| Interslice gap (mm) | 6.5                         | 6.0                           | 6.5                         | 4.4                         | 5.0     |
| 3D T1 GRE\(^{+}\) |                               |                               |                             |                             |         |
| TE (ms)           | 4                             | 2.44                          | 5                           | 2.5                         | 4       |
| TR (ms)           | 1900                          | 5.33                          | 9                           | 1900                        | 8       |
| Flip angle        | 15°                           | 10°                           | 20°                         | 9°                          | 8°      |
| Matrix            | 176 \(\times\) 256            | 192 \(\times\) 192            | 512 \(\times\) 512          | 256 \(\times\) 256          | 256 \(\times\) 256 |
| FOV               | 176 \(\times\) 256            | 250 \(\times\) 250            | 250 \(\times\) 250          | 240 \(\times\) 240          | 240 \(\times\) 240 |
| Pixel size (mm)   | 1 \(\times\) 1               | 1.3 \(\times\) 1.3            | 0.5 \(\times\) 0.5          | 0.9 \(\times\) 0.9          | 0.9 \(\times\) 0.9 |
| No. of slices     | 160                           | 112                           | 161                         | 160                         | 160     |
| Slice thickness (mm) | 1                           | 1.4                           | 1                           | 1                           | 1       |

2D T1 SE\(^{+}\), 2-dimensional post-contrast T1-weighted spin echo with flow compensation; 3D T1 GRE\(^{+}\), 3-dimensional post-contrast T1-weighted gradient echo; FOV, field of view; TE, echo time; TR, repetition time.

**Table 2**

| Variable | All | Lung | Skin | Breast | GU | CUP | GI | Sarcoma |
|----------|-----|------|------|--------|----|-----|----|---------|
| No. of patients | 100 | 51   | 17   | 10     | 10 | 6   | 4  | 2       |
| No. of BM     | 809 | 312  | 199  | 146    | 42 | 47  | 41 | 22      |
| Supratentorial | 580 | 191  | 187  | 71     | 32 | 43  | 35 | 21      |
| Infratentorial | 229 | 121  | 12   | 75     | 10 | 4   | 6  | 1       |
| Necrotic changes of BM | 184 | 86   | 29   | 11     | 16 | 21  | 6  | 13      |

BM, brain metastasis; CUP, cancer of unknown primary; GI, gastrointestinal primary tumor; GU, genitourinary primary tumor; No., number.
(9.3 ± 0.9 vs. 9.2 ± 0.9 s, p < 0.001) were higher in BMpos than within BMneg.

When studying perfusion values for the supratentorial and infratentorial areas separately, we found a marked difference: supratentorial BM occurred more often in areas with lower CBF (51 ± 33 vs. 58 ± 35 ml/100 g/min, p < 0.001) and CBV (3.3 ± 1.9 vs. 3.7 ± 2.1 ml/100 g, p < 0.001) and higher MTT (4.6 ± 0.8 vs. 4.5 ± 0.8 s, p < 0.001) and TTP (9.3 ± 1.1 vs. 9.1 ± 1.1 s, p < 0.001) indicating lower perfusion compared to BMneg. On the contrary, infratentorial BM favored areas with higher CBF (55 ± 33 vs. 39 ± 29 ml/100 g/min, p < 0.001) and CBV (3.7 ± 2.0 vs. 2.7 ± 1.9 ml/100 g, p < 0.001) and shorter MTT (4.7 ± 0.7 vs. 4.7 ± 0.6 s, p < 0.001) and TTP (9.4 ± 0.6 vs. 9.6 ± 0.7 s, p < 0.001) implying higher perfusion compared to BMneg (Figures 3A–D).

Supratentorially, these differences were found to be greater when adjusting for the number of BM occurring within a voxel: in voxels containing a high number of BM the median CBF was even lower compared to the median CBF in all supratentorial voxels.

On the contrary, the highest CBF values infratentorially were observed in voxels containing less BM (Figures 4A,B).

**Perfusion and Central Necrosis**

BM with central necrosis showed a lower CBF (53 ± 33 vs. 59 ± 35 ml/100 g/min, p < 0.001) and CBV (3.5 ± 2.0 vs. 3.9 ± 2.1 ml/100 g, p < 0.001) and higher MTT (4.8 ± 0.8 vs. 4.7 ± 0.7 s, p = 0.002) compared to BM without necrosis. The difference for TTP was not significant (9.4 ± 0.6 vs. 9.3 ± 0.6 s, p = 0.182).

**DISCUSSION**

In a cohort of 100 untreated BM patients we were able to demonstrate an inverse relationship between BM location and brain perfusion depending on lesion location. BM development in proportionally higher perfused areas occurred infratentorially whereas supratentorial BM favored lower-perfused areas. Supratentorial, these results were strengthened by our finding that the difference in perfusion increased with the number of metastases per brain voxel. Furthermore, we found that BM with central necrosis more often developed in areas with lower blood flow that corresponds to the pathophysiology of tumor necrosis.

The observed differences in BM location were greater for CBF and CBV and only marginal for MTT and TTP. This is likely due to the greater physiological heterogeneity of CBF and CBV between anatomical and structural brain regions whereas MTT
and TTP values of the gray and white matter are comparatively similar and do not show large variance throughout the brain (16). But what structural differences may explain our opposite supra- and infratentorial perfusion patterns? One important difference is that in evolutionary terms, the cerebellum and brainstem are older compared to the cerebral neocortex what involves a characteristic vascular architecture (17). De Reuck et al. showed that there is only one type of cerebellar cortical arterial branches whereas the vascularization of the neocortex is more complex and the type of cortical branch is cell layer-dependent (18). Furthermore, one could hypothesize that the perfusion differences are primary due to hemodynamic mechanisms. The vessel cross sectional area of the vertebral arteries is much smaller compared to the internal carotid arteries; therefore, less blood volume arrives infratentorially. Hence, higher perfusion might be a requirement for the development of cerebellar BM. We found the differences in median CBF and CBV of $BM_{pos}$ and $BM_{neg}$ for infratentorial BM being much greater compared to supratentorial BM what may support this hypothesis further.

Preclinical studies showed that the process of metastatic spread to the brain in lung adenocarcinoma and breast cancer cells requires production of vascular endothelial growth factor-A (VEGF-A) that induces early neoangiogenesis whereas metastatic melanoma cells were shown to proliferate along pre-existing and remodeled vessels (vessel cooption) independently from VEGF-A (19–21). Hence, our study findings could indicate that supratentorial BM rely more on VEGF-A-mediated mechanisms of angiogenesis compared to infratentorial BM.

**LIMITATIONS**

The main limitation of our study—since the results imply a relationship between brain perfusion and the occurrence of BM—is that it is unclear whether the perfusion preferences also existed in the individual BM patient because it was derived from a mean perfusion map template. For this purpose, additional perfusion imaging on serial brain MRI for staging purposes could be performed in future clinical studies. However, since Nudelman et al. already demonstrated alterations of the cerebral perfusion in non-metastatic breast cancer patients, this will be difficult to interpret (9). In addition, interindividual as well as longitudinal comparison would be limited.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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