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Associations Between ADC Texture Analysis and Tumor Infiltrating Lymphocytes in Brain Metastasis – A Preliminary Study

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Abstract. *Background/Aim: Tumor infiltrating lymphocytes (TILs) are an important prognostic factor in brain metastasis (BM). This study elucidated associations between apparent diffusion coefficient (ADC) texture analysis and TIL in BM. Patients and Methods: Eleven patients with BM were retrospectively included into the study. TIL levels were analyzed with Leucocyte-common antigen staining. Clinical routine magnetic resonance imaging was used to calculate the texture features. Results: ADC GrayLevelNonUniformity correlated with TILs of the stromal compartment (r=0.67, p=0.02). ADC HighGrayLevelRunEmphasis and ADC Coarseness showed associations with TILs of the tumoral compartment (r=-0.60, p=0.04 and r=0.68, p=0.02, respectively). Conclusion: ADC texture features correlated with TIL levels in BM. ADC texture features could aid in reflecting the complex tumor-micromilieu in a non-invasive manner.*

Brain metastasis (BM) is the most common intracerebral malignancy with still a poor prognosis and a median survival of 6 months (1-3). BM represents a heterogeneous tumor group caused by various primary tumors. The common primary tumors comprise lung cancer, breast cancer and malignant melanoma in this order (1).

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The levels of tumor infiltrating lymphocytes (TIL) are known to be of prognostic relevance in BM (4). Berghoff *et al*. showed that CD8+-TIL levels were associated with perifocal edema and with a better median overall survival of BM patients (4). Moreover, TIL levels are also highlighted as an important prognostic marker in several tumor entities throughout oncology (5-7).

Diffusion-weighted imaging (DWI) is a functional imaging sequence, which reflects random water movement (8, 9). The apparent diffusion coefficient (ADC) is the quantification of this water movement. In various investigations, it was shown that ADC value is inversely correlated with cellularity and other important histopathological features in several tumors (8-13).

Regarding BM, the ADC values show a relatively wide range in different primary tumors with corresponding different underlying histological composition (14-18). Nevertheless, ADC values were of prognostic relevance in several studies, which highlights the importance of this imaging sequence in BM (15, 16, 19).

For BM, there is data that ADC values are inversely associated with cell density and cellularity (15, 17). Notably, for BM of lung cancers there were statistically significant differences between EGFR positive and negative tumors (20).

To further analyzed ADC values, texture analysis can be employed, which is a method to quantify the spatial heterogeneity of the ADC values in a defined region of interest (21, 22). With this method, various parameters can be calculated, which show also different correlations with the underlying histopathology of tumors (22).

However, little is known regarding the associations between ADC texture analysis and TIL expression in BM.

Therefore, the purpose of the present study was to elucidate whether TIL levels in surgical specimens are

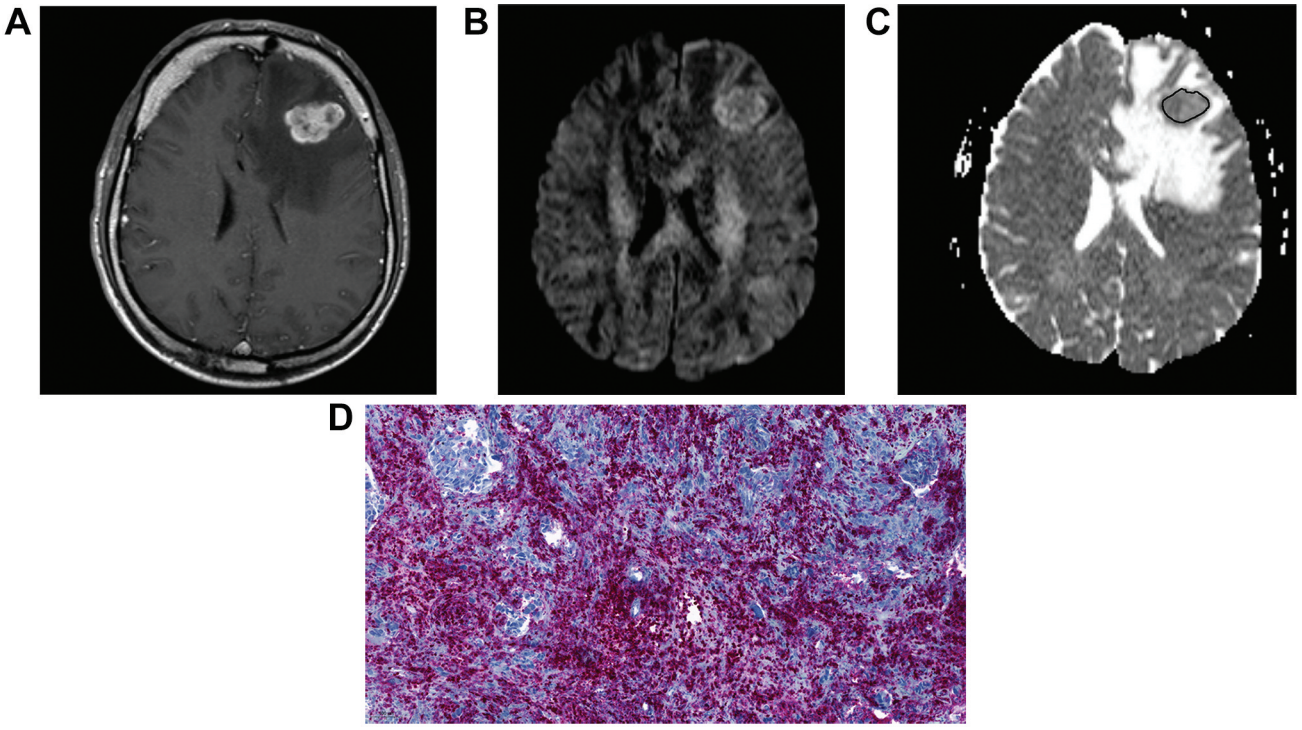

Figure 1. *Representative case of a patient sample with a known non-small cell cancer of the lung and a brain metastasis located in the left frontal lobe. A. Postcontrast T1-weighted image in axial plane. A strong contrast media enhancement can be appreciated with small central necrosis. A severe surrounding edema can also be observed. B. The corresponding DWI image of this patients (b-value of 1,000 s/mm^2). C. The corresponding apparent diffusion coefficient map with a drawn ROI. The measurement was performed as a whole lesion measurement on every tumor displaying slide. D. The Leucocyte common antigen-stained specimen of this patient. The tumor infiltrating lymphocyte levels in the tumor are 40 per high-power field and in the stromal compartment is 80 per high-power field.*

associated with ADC texture parameters of BM calculated by routinely obtained MRI.

Patients and Methods

This study was approved by the institutional review board (Ethic committee of the University of Leipzig) and informed consent was waived. The radiological database of the university hospital was retrospectively screened for patients with BM between 2016 and 2017.

The following inclusion criteria were defined: magnetic resonance imaging (MRI) of the head including DWI sequence– and available histopathology specimen acquired by surgical resection. The following exclusion criteria were defined: previous systemic or local treatment of BM– and insufficient image quality

Patients. Overall, 11 patients with BM were included into the present study. There were 5 (45.5%) women and 6 (55.5%) men with a mean age of 57.1±14.7 years, range=28-78 years.

Imaging acquisition. MRI was performed for surgical planning in clinical routine using a 1.5T scanner (Aera 1.5T, Siemens, Erlangen, Germany) with a standard head coil. DWI was obtained as a multi-slice single-shot echo-planar imaging sequence (TR/TE: 5,900/96 ms; FOV: 250×250 mm; slice thickness: 5 mm; acquisition matrix: 128×128. B-values of 0, 500, and 1,000 s/mm^2 were used.

Image analysis. The images were analyzed by a neuroradiology resident (G.P., 5 years of neuroradiology experience) blinded to the histopathology. Texture analysis was performed using validated software (23, 24), resulting in 95 features per case. A polygonal volume of interest (VOI) was placed on all tumor displaying slides according to the boundaries of the T1w contrast media enhancement. Gray-level normalization was performed to minimize the influence of contrast and brightness variation (μ±3 SD), as previously performed (25). Figure 1 displays a representative patient of our cohort.

Histopathology analysis. The diagnosis was confirmed by histopathology after tumor resection in every case. Histopathology analysis was performed by an experienced board-certified pathologist (A.K.H.) with 14 years of experience blinded to the imaging results. The histological specimens were deparaffinized, rehydrated, and cut into 5 μm slices. First, the standard Hematoxylin and eosin (HE) staining was evaluated. Then, the histological slices were stained for Leucocyte common antigen (LCA) (CD45, DAKO, dilution 1:150). All histopathology quantifications were performed on a 20-fold magnification. TIL levels were evaluated per high power field.

Statistical analysis. Statistics and graphics creation was performed with Graph Pad Prism 5 (GraphPad Software, La Jolla, CA, USA).

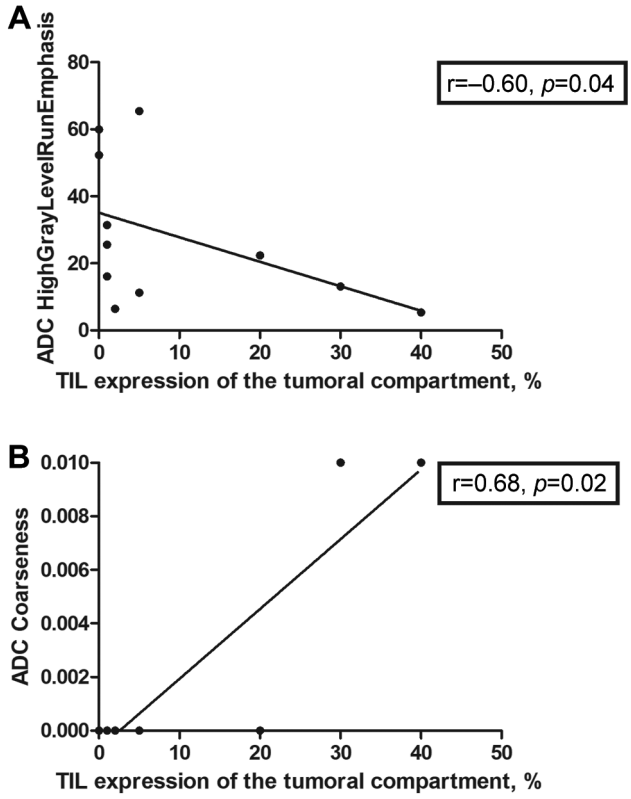

Figure 2. *Correlation analysis between apparent diffusion coefficient (ADC) texture analysis and tumor infiltrating lymphocyte (TIL) levels of the tumoral compartment. A. Spearman's correlation analysis between ADC. HighGrayLevelRunEmphasis and TIL levels in the tumoral compartment (r=–0.60, p=0.04). B. Spearman's correlation analysis between ADC Coarseness and TIL levels in the tumoral compartment (r=0.68, p=0.02).*

Collected data were evaluated by means of descriptive statistics. For correlation analysis, Spearman's correlation coefficient (r) was used to analyze possible associations for the investigated parameters. Mann-Whitney test was used for group discrimination analysis. In every instance, p-values <0.05 were taken to indicate statistical significance.

Results

The tumors were localized supratentorial in 8 cases (72.7%) and infratentorial in 3 cases (17.3%).

Primary tumors were as follows: 7 patients had non-small cell lung cancer (NSCLC) (63.6%), one patient (9.1%) had colorectal cancer, urothelial cancer, malignant melanoma, and nasopharynx carcinoma, respectively.

The mean TIL levels of the tumoral compartment were 9.5±13.9% and of the stromal compartment 44.4±24.9%. TIL levels in the stromal compartment were significantly higher than TIL levels in the tumor compartment (p=0.001).

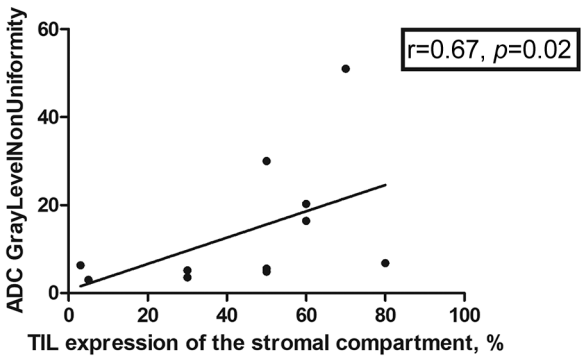

Figure 3. *Spearman's correlation analysis between apparent diffusion coefficient GrayLevelNonUniformity and tumor infiltrating lymphocyte expression of the stromal compartment (r=0.67, p=0.02).*

The correlation analysis between TIL levels in the tumor compartment revealed statistically significant correlations with ADC HighGrayLevelRunEmphasis and ADC Coarseness (r=-0.60, p=0.04 and r=0.68, p=0.02, respectively; Figure 2).

TIL levels in the stromal compartment were correlated significantly with ADC GrayLevelNonUniformity (r=0.67, p=0.02). Figure 3 displays the corresponding correlation graph.

Discussion

The present study analyzed associations between ADC texture analysis and TIL levels in BM. Presumably, ADC texture analysis can reflect complex tissue compositions of the tumor micromilieu. As shown, different ADC texture features seem to reflect TIL levels in tumoral and stromal compartments. However, there is definite need to confirm the present results in a larger patient sample.

Only few studies investigated possible associations between imaging and histopathology features in BM (15-17, 26-29). In a noteworthy study, Berghoff *et al*. have investigated the role of different TIL subtypes in patients with BM undergoing surgery (4). One key finding was that CD8+ lymphocytes were inversely associated with the extension of perifocal edema, being more expressed in the patients with less edema (4). Other subtypes including CD3+, CD45RO+, FOXP3+ and PD1+ TIL subtypes were not correlated with edema extension (4). As another key finding of this study, CD3+, CD8+ and CD45RO+ TIL levels were associated with survival, even in multivariate analysis (4). In short, increased levels of TIL are associated with a better outcome in BM.

In a first study, Hayashida *et al*. investigated the ADC values of 26 patients with BM and could show a clear inverse correlation between ADC and cellularity (17). In other studies, correlations between cell density, ADC values (15) and signal intensities of the DWI sequence were

identified (16). Of further note, differences in ADC values were identified between different primary tumors with small cell lung cancer showing the lowest ADC values compared to other primary tumors (14). In another study, the frequencies of metastasis displaying a diffusion restriction, defined by hyperintensity of the DWI sequence, was evaluated. This frequency differed significantly between different primary tumors and was primarily identified in patients with lung cancer (18). Importantly, these studies also identified significant associations of ADC values with overall survival in BM (15, 16, 19).

Another study has investigated associations between T-cell densities with ADC metrics in 26 resected BM (29). It was found that only increased density of $CD3^+$ lymphocytes correlated with decreased fraction anisotropy values derived from diffusion tensor imaging (p=0.037). Moreover, the authors concluded that T-cell response to brain metastases is associated with patient survival time regardless of other different biological factors investigated in this study (29).

Interestingly, there are histological differences of the tumor microenvironment between the primary tumor and the BM. Most evidence has been published for lung cancer. It was shown that BM had higher PD1+ TIL compared to the primary tumor (30), whereas CD8+ TIL levels were significantly lower in BM (31).

For renal cell cancer, most TIL subtypes were equally expressed in the primary tumor and the corresponding BM (32). For other primary tumors, no reliable data is available.

ADC texture analysis was employed to discriminate solitary brain metastasis from glioblastoma multiforme (33).

One can assume that virtual biopsy performed by MRI texture analysis can aid to characterize tissue microstructure including the immune microenvironment, especially when combining different MRI sequences in a radiomics signature. This was shown in another study on glioblastoma in which different sequences could reflect distinctive tissue features (34).

There are some limitations to the present analysis. First, it is a retrospective study with possible inherent bias. However, imaging and histopathology were performed independently and blindly. This should reduce possible bias. Second, the study design allowed only the inclusion of surgical resected metastases. There might be resulting selection bias. Third, the patient sample is small and compared to other patient samples, cases of breast cancer and malignant melanoma patients are underrepresented.

In conclusion, ADC texture parameters could aid in reflecting the complex tumor-micromilieu in a non-invasive manner. Different ADC texture features seem to reflect TIL levels in tumoral and stromal compartment.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

Study design: Hans-Jonas Meyer, Alexey Surov; Data collection: Gordian Prasse, Anne Kathrin Höhn; Data processing: Hans-Jonas Meyer, Gordian Prasse, Anne Kathrin Höhn, Karl-Titus Hoffmann; Article preparation and review: Hans-Jonas Meyer, Alexey Surov.

References

1 Gavrilovic IT and Posner JB: Brain metastases: epidemiology and pathophysiology. J Neurooncol *75(1)*: 5-14, 2005. PMID: 16215811. DOI: 10.1007/s11060-004-8093-6

2 Ekici K, Temelli O, Dikilitas M, Halil Dursun I, Bozdag Kaplan N and Kekilli E: Survival and prognostic factors in patients with brain metastasis: Single center experience. J BUON *21(4)*: 958-963, 2016. PMID: 27685920.

3 Saito EY, Viani GA, Ferrigno R, Nakamura RA, Novaes PE, Pellizzon CA, Fogaroli RC, Conte MA and Salvajoli JV: Whole brain radiation therapy in management of brain metastasis: results and prognostic factors. Radiat Oncol *1*: 20, 2006. PMID: 16808850. DOI: 10.1186/1748-717X-1-20

4 Berghoff AS, Fuchs E, Ricken G, Mlecnik B, Bindea G, Spanberger T, Hackl M, Widhalm G, Dieckmann K, Prayer D, Bilocq A, Heinzl H, Zielinski C, Bartsch R, Birner P, Galon J and Preusser M: Density of tumor-infiltrating lymphocytes correlates with extent of brain edema and overall survival time in patients with brain metastases. Oncoimmunology *5(1)*: e1057388, 2015. PMID: 26942067. DOI: 10.1080/2162402X.2015.1057388

5 Schoenberg MB, Li X, Li X, Han Y, Hao J, Miksch RC, Koch D, Börner N, Beger NT, Bucher JN, Schiergens TS, Guba MO, Werner J and Bazhin AV: The predictive value of tumor infiltrating leukocytes in Hepatocellular Carcinoma: A systematic review and meta-analysis. Eur J Surg Oncol, 2021. PMID: 33966947. DOI: 10.1016/j.ejso.2021.04.042

6 Tan HNC, Catedral LIG and San Juan MD: Prognostic significance of tumor-infiltrating lymphocytes on survival outcomes of patients with resected pancreatic ductal adenocarcinoma: A systematic review and meta-analysis. J Immunother *44(1)*: 29-40, 2021. PMID: 32909965. DOI: 10.1097/CJI.0000000000000331

7 García-Marín R, Reda S, Riobello C, Cabal VN, Suárez-Fernández L, Vivanco B, Álvarez-Marcos C, López F, Llorente JL and Hermsen MA: Prognostic and therapeutic implications of immune classification by $CD8^+$ tumor-infiltrating lymphocytes and PD-L1 expression in sinonasal squamous cell carcinoma. Int J Mol Sci *22(13)*: 6926, 2021. PMID: 34203211. DOI: 10.3390/ijms22136926

8 Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, Dzik-Jurasz A, Ross BD, Van Cauteren M, Collins D, Hammoud DA, Rustin GJ, Taouli B and Choyke PL: Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia *11(2)*: 102-125, 2009. PMID: 19186405. DOI: 10.1593/neo.81328

9 Surov A, Meyer HJ and Wienke A: Correlation between apparent diffusion coefficient (ADC) and cellularity is different in several tumors: a meta-analysis. Oncotarget *8(35)*: 59492-59499, 2017. PMID: 28938652. DOI: 10.18632/oncotarget.17752

10 Meyer HJ, Höhn AK and Surov A: Associations between ADC and tumor infiltrating lmphocytes, tumor-stroma ratio and

vimentin expression in head and neck squamous cell cancer. Acad Radiol, 2021. PMID: 34217611. DOI: 10.1016/j.acra.2021.05.007

11 Meyer HJ, Gundermann P, Höhn AK, Hamerla G and Surov A: Associations between whole tumor histogram analysis parameters derived from ADC maps and expression of EGFR, VEGF, Hif 1-alpha, Her-2 and Histone 3 in uterine cervical cancer. Magn Reson Imaging *57*: 68-74, 2019. PMID: 30367998. DOI: 10.1016/j.mri.2018.10.016

12 Park YW, Park JE, Ahn SS, Kim EH, Kang SG, Chang JH, Kim SH, Choi SH, Kim HS and Lee SK: Magnetic resonance imaging parameters for noninvasive prediction of epidermal growth factor receptor amplification in isocitrate dehydrogenase-wild-type lower-grade gliomas: a multicenter study. Neurosurgery *89(2)*: 257-265, 2021. PMID: 33913501. DOI: 10.1093/neuros/nyab136

13 Zhao J, Gao S, Sun W, Grimm R, Fu C, Han J, Sheng R and Zeng M: Magnetic resonance imaging and diffusion-weighted imaging-based histogram analyses in predicting glypican 3-positive hepatocellular carcinoma. Eur J Radiol *139*: 109732, 2021. PMID: 33905978. DOI: 10.1016/j.ejrad.2021.109732

14 Meyer HJ, Fiedler E, Kornhuber M, Spielmann RP and Surov A: Comparison of diffusion-weighted imaging findings in brain metastases of different origin. Clin Imaging *39(6)*: 965-969, 2015. PMID: 26253774. DOI: 10.1016/j.clinimag.2015.06.015

15 Zakaria R, Das K, Radon M, Bhojak M, Rudland PR, Sluming V and Jenkinson MD: Diffusion-weighted MRI characteristics of the cerebral metastasis to brain boundary predicts patient outcomes. BMC Med Imaging *14*: 26, 2014. PMID: 25086595. DOI: 10.1186/1471-2342-14-26

16 Berghoff AS, Spanberger T, Ilhan-Mutlu A, Magerle M, Hutterer M, Woehrer A, Hackl M, Widhalm G, Dieckmann K, Marosi C, Birner P, Prayer D and Preusser M: Preoperative diffusion-weighted imaging of single brain metastases correlates with patient survival times. PLoS One *8(2)*: e55464, 2013. PMID: 23393579. DOI: 10.1371/journal.pone.0055464

17 Hayashida Y, Hirai T, Morishita S, Kitajima M, Murakami R, Korogi Y, Makino K, Nakamura H, Ikushima I, Yamura M, Kochi M, Kuratsu JI and Yamashita Y: Diffusion-weighted imaging of metastatic brain tumors: comparison with histologic type and tumor cellularity. AJNR Am J Neuroradiol *27(7)*: 1419-1425, 2006. PMID: 16908550.

18 Duygulu G, Ovali GY, Calli C, Kitis O, Yünten N, Akalin T and Islekel S: Intracerebral metastasis showing restricted diffusion: correlation with histopathologic findings. Eur J Radiol *74(1)*: 117-120, 2010. PMID: 19359117. DOI: 10.1016/j.ejrad.2009.03.004

19 Zakaria R, Chen YJ, Hughes DM, Wang S, Chawla S, Poptani H, Berghoff AS, Preusser M, Jenkinson MD and Mohan S: Does the application of diffusion weighted imaging improve the prediction of survival in patients with resected brain metastases? A retrospective multicenter study. Cancer Imaging *20(1)*: 16, 2020. PMID: 32028999. DOI: 10.1186/s40644-020-0295-4

20 Jung WS, Park CH, Hong CK, Suh SH and Ahn SJ: Diffusion-weighted imaging of brain metastasis from lung cancer: Correlation of MRI parameters with the histologic type and gene mutation status. AJNR Am J Neuroradiol *39(2)*: 273-279, 2018. PMID: 29301782. DOI: 10.3174/ajnr.A5516

21 Incoronato M, Aiello M, Infante T, Cavaliere C, Grimaldi AM, Mirabelli P, Monti S and Salvatore M: Radiogenomic analysis of oncological data: A technical survey. Int J Mol Sci *18(4)*: 805, 2017. PMID: 28417933. DOI: 10.3390/ijms18040805

22 Just N: Improving tumour heterogeneity MRI assessment with histograms. Br J Cancer *111(12)*: 2205-2213, 2014. PMID: 25268373. DOI: 10.1038/bjc.2014.512

23 Aerts HJ, Velazquez ER, Leijenaar RT, Parmar C, Grossmann P, Carvalho S, Bussink J, Monshouwer R, Haibe-Kains B, Rietveld D, Hoebers F, Rietbergen MM, Leemans CR, Dekker A, Quackenbush J, Gillies RJ and Lambin P: Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun *5*: 4006, 2014. PMID: 24892406. DOI: 10.1038/ncomms5006

24 van Griethuysen JJM, Fedorov A, Parmar C, Hosny A, Aucoin N, Narayan V, Beets-Tan RGH, Fillion-Robin JC, Pieper S and Aerts HJWL: Computational radiomics system to decode the radiographic phenotype. Cancer Res *77(21)*: e104-e107, 2017. PMID: 29092951. DOI: 10.1158/0008-5472.CAN-17-0339

25 Fruehwald-Pallamar J, Czerny C, Holzer-Fruehwald L, Nemec SF, Mueller-Mang C, Weber M and Mayerhoefer ME: Texture-based and diffusion-weighted discrimination of parotid gland lesions on MR images at 3.0 Tesla. NMR Biomed *26(11)*: 1372-1379, 2013. PMID: 23703801. DOI: 10.1002/nbm.2962

26 Spanberger T, Berghoff AS, Dinhof C, Ilhan-Mutlu A, Magerle M, Hutterer M, Pichler J, Wöhrer A, Hackl M, Widhalm G, Hainfellner JA, Dieckmann K, Marosi C, Birner P, Prayer D and Preusser M: Extent of peritumoral brain edema correlates with prognosis, tumoral growth pattern, HIF1a expression and angiogenic activity in patients with single brain metastases. Clin Exp Metastasis *30(4)*: 357-368, 2013. PMID: 23076770. DOI: 10.1007/s10585-012-9542-9

27 Meyer HJ, Hamerla G, Höhn AK, Hoffmann KT and Surov A: Perifocal edema volume is not associated with immunohistochemical features reflecting proliferation potential, microvessel density, neoangiogenesis and invasiveness in brain metastasis. Clin Neurol Neurosurg *202*: 106537, 2021. PMID: 33571782. DOI: 10.1016/j.clineuro.2021.106537

28 Fiss I, Hussein A, Barrantes-Freer A, Sperling S, Hernandez-Duran S, Wolfert C, Pukrop T, Ninkovic M, Bleckmann A, Rohde V, Mielke D and Schatlo B: Cerebral metastases: do size, peritumoral edema, or multiplicity predict infiltration into brain parenchyma? Acta Neurochir (Wien) *161(5)*: 1037-1045, 2019. PMID: 30877471. DOI: 10.1007/s00701-019-03842-3

29 Zakaria R, Platt-Higgins A, Rathi N, Radon M, Das S, Das K, Bhojak M, Brodbelt A, Chavredakis E, Jenkinson MD and Rudland PS: T-cell densities in brain metastases are associated with patient survival times and diffusion tensor MRI changes. Cancer Res *78(3)*: 610-616, 2018. PMID: 29212855. DOI: 10.1158/0008-5472.CAN-17-1720

30 Kim R, Keam B, Kim S, Kim M, Kim SH, Kim JW, Kim YJ, Kim TM, Jeon YK, Kim DW, Chung DH, Lee JS and Heo DS: Differences in tumor microenvironments between primary lung tumors and brain metastases in lung cancer patients: therapeutic implications for immune checkpoint inhibitors. BMC Cancer *19(1)*: 19, 2019. PMID: 30616523. DOI: 10.1186/s12885-018-5214-8

31 Zhou J, Gong Z, Jia Q, Wu Y, Yang ZZ and Zhu B: Programmed death ligand 1 expression and $CD8^+$ tumor-infiltrating lymphocyte density differences between paired primary and brain metastatic lesions in non-small cell lung cancer. Biochem Biophys Res Commun *498(4)*: 751-757, 2018. PMID: 29526752. DOI: 10.1016/j.bbrc.2018.03.053

32 Steindl A, Alpar D, Heller G, Mair MJ, Gatterbauer B, Dieckmann K, Widhalm G, Hainfellner JA, Schmidinger M, Bock C, Müllauer L, Preusser M and Berghoff AS: Tumor mutational burden and immune infiltrates in renal cell carcinoma and matched brain metastases. ESMO Open *6(2)*: 100057, 2021. PMID: 33588158. DOI: 10.1016/j.esmoop.2021.100057

33 Zhang G, Chen X, Zhang S, Ruan X, Gao C, Liu Z and Wei X: Discrimination between solitary brain metastasis and glioblastoma multiforme by using ADC-based texture analysis: A comparison of two different ROI placements. Acad Radiol *26(11)*: 1466-1472, 2019. PMID: 30770161. DOI: 10.1016/j.acra.2019.01.010

34 Chang PD, Malone HR, Bowden SG, Chow DS, Gill BJA, Ung TH, Samanamud J, Englander ZK, Sonabend AM, Sheth SA, McKhann GM 2nd, Sisti MB, Schwartz LH, Lignelli A, Grinband J, Bruce JN and Canoll P: A multiparametric model for mapping cellularity in glioblastoma using radiographically localized biopsies. AJNR Am J Neuroradiol *38(5)*: 890-898, 2017. PMID: 28255030. DOI: 10.3174/ajnr.A5112

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