

Histogram Profiling of Postcontrast T1-Weighted MRI Gives Valuable Insights into Tumor Biology and Enables Prediction of Growth Kinetics and Prognosis in Meningiomas^{1,2}



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Abstract

BACKGROUND: Meningiomas are the most frequently diagnosed intracranial masses, oftentimes requiring surgery. Especially procedure-related morbidity can be substantial, particularly in elderly patients. Hence, reliable imaging modalities enabling pretherapeutic prediction of tumor grade, growth kinetic, realistic prognosis, and—as a consequence—necessity of surgery are of great value. In this context, a promising diagnostic approach is advanced analysis of magnetic resonance imaging data. Therefore, our study investigated whether histogram profiling of routinely acquired postcontrast T1-weighted images is capable of separating low-grade from high-grade lesions and whether histogram parameters reflect Ki-67 expression in meningiomas. **MATERIAL AND METHODS:** Pretreatment T1-weighted postcontrast volumes of 44 meningioma patients were used for signal intensity histogram profiling. WHO grade, tumor volume, and Ki-67 expression were evaluated. Comparative and correlative statistics investigating the association between histogram profile parameters and neuropathology were performed. **RESULTS:** None of the investigated histogram parameters revealed significant differences between low-grade and high-grade meningiomas. However, significant correlations were identified between Ki-67 and the histogram parameters skewness and entropy as well as between entropy and tumor volume. **CONCLUSIONS:** Contrary to previously reported findings, pretherapeutic postcontrast T1-weighted images can be used to predict growth kinetics in meningiomas if whole tumor histogram analysis is employed. However, no differences between distinct WHO grades were identifiable in our cohort. As a consequence, histogram analysis of postcontrast T1-weighted images is a promising approach to obtain quantitative *in vivo* biomarkers reflecting the proliferative potential in meningiomas.

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Introduction

Considering all central nervous system (CNS) and brain tumors, meningiomas are the most frequently diagnosed intracranial masses and comprise more than one third of all entities [1]. According to the WHO classification and grading system of CNS tumors, there are three groups of meningiomas: benign (grade I), atypical (grade II), and anaplastic (grade III) [2]. Among these different groups, low-grade meningiomas (WHO I), with approximately 80%–90% of all

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cases, by far constitute the largest proportion [3, 4]. They are associated with lower recurrence rates after surgery and better overall prognosis compared to high-grade meningiomas (WHO grade II and III) [5, 6].

Gross total resection including the infiltrated dura mater is still the standard treatment of diagnosed meningiomas [7]. However, depending on the location and extension of the tumor, surgery may be associated with considerable surgical complication rates and thus with higher overall mortality especially in elderly patients [8]. This and the fact that a significant fraction of all meningiomas remains asymptomatic and is discovered incidentally highlight the requirement of reliable imaging modalities, particularly in terms of predicting tumor grade, growth kinetics, and other prognostic biomarkers to prevent unnecessary surgery.

Up to now, magnetic resonance imaging (MRI) and the visual evaluation of macroscopic tumor characteristics assessed *via* routinely used MRI sequences, more specifically T1-weighted, T2-weighted, and gadolinium-enhanced sequences, are still the gold standard of the pretherapeutic diagnostics [7]. Although morphological key features like tumor-brain interface, capsular enhancement, or heterogeneous tumor enhancement were shown to be of potential value in differentiation between low-grade and high-grade meningiomas [9, 10], traditional MRI diagnostic remains a subjective and consecutively observer-dependent method requiring experience and expertise of the observing radiologist. One possible approach to decrease intra- and interobserver variability in this regard is to simply quantify mean signal intensities using region of interest (ROI) analysis. However, concerning meningiomas, this method unveiled neither significant differences between low- and high-grade meningiomas nor a correlation with Ki-67 expression representing proliferative activity [11].

An increasingly performed and certainly promising approach of processing and quantifying MRI data in an objective manner is histogram analysis (HA) of whole lesion volumes [12]. A variety of recent investigations exemplarily showed the potential of HA to predict tumor biology using elaborate functional imaging techniques like diffusion-weighted imaging, which notoriously reflects underlying tissue microarchitecture [12–18]. Furthermore, the value of HA in the neuro-oncological workflow to distinguish morphologically similar mass lesions has been demonstrated [19]. However, investigations using histogram analysis of conventional MR imaging data are sparse [20].

Therefore, the aim of this study was to evaluate whether whole tumor histogram profiling of preoperative contrast-enhanced T1-weighted images has the capability to 1) reflect the prognostically relevant Ki-67 expression, representing the cell proliferation kinetics of the corresponding lesion, and 2) differentiate between low-grade and high-grade meningiomas.

Patients, Procedures, and Methods

Ethics Approval

The study was approved by the ethics committee of the medical council of Baden-Württemberg (Ethik-Kommission Landesärztekammer Baden-Württemberg, F-2017-047).

Patients Collective

The institutional radiological information system was searched for patients with the diagnosis meningioma. Fifty-six patients were

identified between 01/2012 and 08/2017, all of which had surgery with at least partial removal of the tumor in our hospital and subsequent neuropathological workup. Only patients who received pretreatment MRI scans with sufficient quality of the T1-weighted spin echo sequences after intravenous application of contrast medium were included. MRI examinations of patients indicating hemorrhage or significant calcifications were excluded since these conditions severely influence quantification of the signal intensities. Therefore, only 44 patients (37 females, 7 males; ranging from 40 to 87 years with a mean age of 61.4 years) were included in our retrospective analysis.

MRI Specifics

For all patients, MRI of the brain was performed using a 1.5-T device (MAGNETOM Aera, MAGNETOM Symphony and MAGNETOM Sonata; Tx/Rx CP head coil, Siemens, Erlangen, Germany). The imaging protocol included the following sequences:

- Axial T1-weighted (T1w) spin echo (SE) sequences (TR/TE: 453/17, flip angle: 90°, slice thickness: 5 mm, acquisition matrix: 320×179, field of view: 230×187 mm) prior and post intravenous application of contrast medium (Gadobutrol, Gadovist, Bayer Schering Pharma, Leverkusen, Germany)

All images were available in digital form and analyzed by two experienced radiologists (G.A.G., S.S.) without knowledge of the histopathological diagnosis on a PACS workstation (Impax EE R20 XII).

Histogram Profiling of T1-Weighted Postcontrast Images

T1-weighted postcontrast images were exported from our institutional archive in DICOM format *via* the aforementioned AGFA PACS. Using a custom-made DICOM image analysis tool (programmed using Matlab, The Mathworks, Natick, MA), whole lesion histogram profiling was performed as follows: T1-weighted postcontrast images of each patient were loaded into a graphical user interface, and ROIs of the whole contrast enhancing lesion were manually drawn. The histogram profile was consecutively calculated, providing the following set of parameters: SImean, SImin, SImax, SIp10, SIp25, SIp75, SIp90, SImodus, SImedian, skewness, kurtosis, and entropy.

Neuropathology

All tumor specimens were used for neurohistological confirmation of the diagnosis. A 5- μ m section of each tumor was stained by H&E, and two further sections were employed for Ki-67 immunohistochemistry to determine the proliferation rate of each tumor, as previously reported [21]. The histopathological images were digitalized with a Jenalumar microscope carrying a 4.2 digital camera (Zeiss, Jena, Germany). Thereupon, Ki-67 index was quantified using the ImageJ particles tool as described previously [12].

Statistical Analysis

Statistical analysis including graphics creation was performed using SPSS 24.0 (SPSS Inc., Chicago, IL). In a first step, SI data and histopathological information were investigated using descriptive statistics. In a second step, data were tested for homogeneity of variance (homoscedasticity) using Levene's test. *t* test was performed to compare evaluated, homoscedastic parameters of SI histogram profiling between low-grade and high-grade meningiomas. Mann-Whitney *U* test was performed to compare parameters exhibiting

heteroscedastic data between low-grade and high-grade meningiomas. Finally, correlation analysis for homoscedastic parameters was performed using Pearson correlation coefficient. In case of heteroscedastic data, Spearman-Rho rank-order correlation was calculated. *P* values < .05 were taken to indicate statistical significance in all instances.

Results

Figure 1 shows examples of cranial MRI from patients with low-grade (upper case) and high-grade meningiomas (lower case) with the corresponding whole tumor SI histogram and the Ki-67 immunohistochemical staining.

The results of the descriptive analysis of SI data and histopathological information are summarized in Table 1. Levene’s test revealed homoscedasticity of the data for SI_{mean}, SI_{min}, SI_{max}, SI_{p10}, SI_{p25}, SI_{p75}, SI_{p90}, SI_{modus}, SI_{median}, entropy, kurtosis, skewness, and tumor volume. Heteroscedasticity was determined for Ki-67.

Consequently, (unpaired) *t* test was used to compare SI_{mean}, SI_{min}, SI_{max}, SI_{p10}, SI_{p25}, SI_{p75}, SI_{p90}, SI_{modus}, SI_{median}, entropy, kurtosis, skewness, and tumor volume between low-grade and high-grade meningiomas. Mann-Whitney *U* test was used to compare Ki-67 between low-grade and high-grade meningiomas. In brief, neither the investigated signal intensity histogram parameters nor the tumor volume revealed significant differences between low-grade and high-grade meningiomas. As expected, high-grade meningiomas showed statistically significant higher Ki-67 expression than low-grade meningiomas, representing the proliferative activity of the tumor. The complete results of the comparative statistical analysis are given in Table 2.

Table 1. Tumor Volume and SI Histogram Parameters of All Investigated Meningiomas

Parameters	Mean ± Standard Deviation	Minimum	Maximum
Lesion volume × 10 ³ mm ³	25.82 ± 21.08	3.20	8.13
SI _{mean}	655.32 ± 181.55	393.00	1270.00
SI _{min}	191.66 ± 105.80	1.00	449.00
SI _{max}	1002.52 ± 263.12	608.00	1746.00
P10 SI	524.81 ± 173.67	237.00	1021.00
P25 SI	605.40 ± 186.86	349.00	1206.00
P75 SI	720.66 ± 200.21	433.00	1444.00
P90 SI	757.30 ± 208.53	453.00	1513.00
Median SI	671.55 ± 191.51	404.00	1362.00
Mode SI	664.56 ± 216.70	255.00	1415.00
Kurtosis	6.52 ± 3.32	1.37	15.34
Skewness	-1.00 ± 0.74	-2.74	0.46
Entropy	4.29 ± 0.57	2.97	5.53

Table 2. Comparison of SI Histogram Profiles, Ki-67 Index, and Lesion Volume between Low-Grade and High-Grade Meningiomas

Parameters	Low-Grade Mean ± SD	High-Grade Mean ± SD	<i>P</i> Values
SI _{mean}	680.61 ± 168.89	574.04 ± 183.54	.496
SI _{min}	197.26 ± 102.33	154.30 ± 103.00	.890
SI _{max}	1023.00 ± 264.31	915.20 ± 229.86	.716
P10 SI	548.63 ± 154.35	436.64 ± 177.98	.500
P25 SI	632.54 ± 174.04	514.78 ± 187.81	.430
P75 SI	747.08 ± 191.60	641.70 ± 205.89	.527
P90 SI	783.70 ± 201.85	677.47 ± 214.88	.536
Median SI	695.78 ± 183.09	598.70 ± 192.38	.589
Mode SI	692.06 ± 210.51	576.50 ± 214.96	.521
Kurtosis	6.90 ± 3.41	6.01 ± 3.66	.686
Skewness	-1.15 ± 0.72	-0.72 ± 0.74	.151
Entropy	4.22 ± 0.58	4.38 ± 0.53	.221
Ki-67	4.59 ± 2.56	11.80 ± 8.77	<.001
Lesion volume × 10 ³ mm ³	22.20 ± 16.81	32.12 ± 28.58	.117

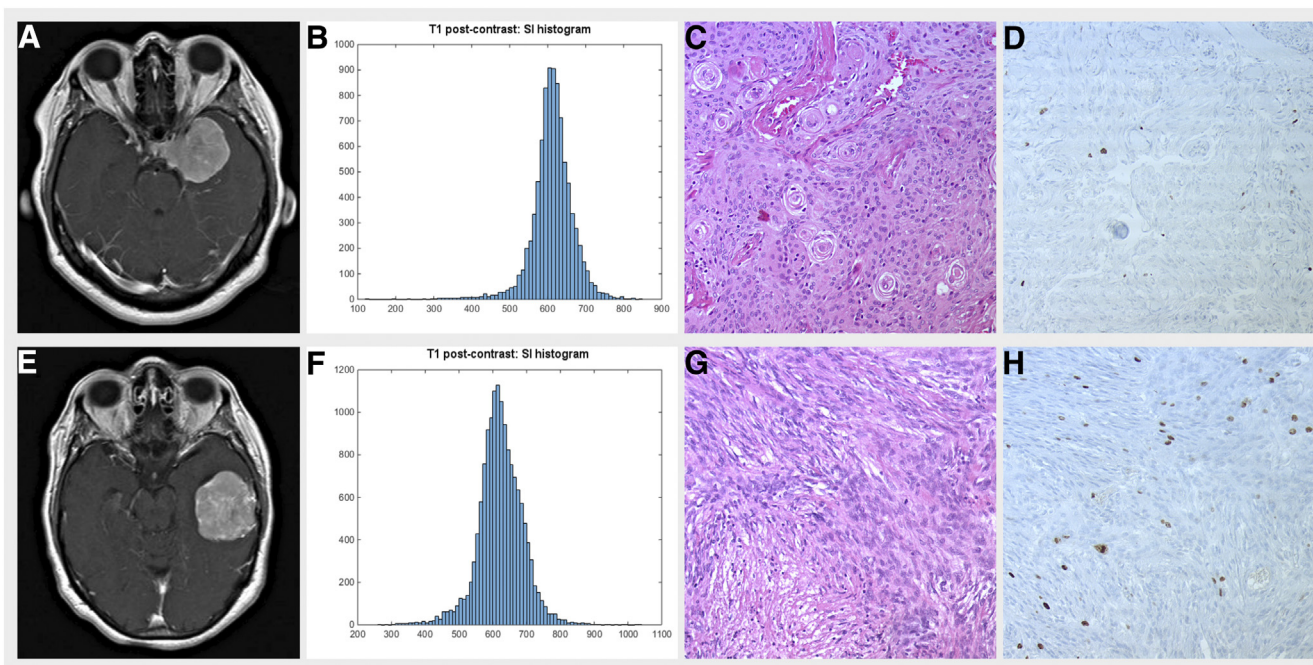


Figure 1. Representative MRI sections, the corresponding whole tumor SI histogram, H&E staining, and Ki-67 immunohistochemistry from a low-grade (A-D) and a high-grade meningioma (E-H). The first image of each case gives the T1-weighted section post gadolinium application, showing the meningioma in its maximum diameter; the second image displays the whole tumor SI histogram (x-axis: SI values in incremental order, y-axis: number of voxels). H&E staining and Ki-67 immunohistochemistry are displayed on the right. For the first case (low-grade meningioma), a proliferation index of 5% was calculated. In the second case (high-grade meningioma), proliferation index was 10%.

Table 3. Correlations between SI Histogram Profile Parameters and Ki-67 and Lesion Volume of All Investigated Meningiomas.

SI Histogram Profile Parameters/Lesion Volume	Ki-67	Lesion Volume
SI _{mean}	<i>r</i> = -0.057 <i>P</i> = .697	<i>r</i> = 0.085 <i>P</i> = .556
SI _{min}	<i>r</i> = -0.036 <i>P</i> = .805	<i>r</i> = -0.069 <i>P</i> = .634
SI _{max}	<i>r</i> = 0.126 <i>P</i> = .389	<i>r</i> = 0.267 <i>P</i> = .061
P10 SI	<i>r</i> = -0.064 <i>P</i> = .663	<i>r</i> = 0.068 <i>P</i> = .638
P25 SI	<i>r</i> = -0.082 <i>P</i> = .575	<i>r</i> = 0.045 <i>P</i> = .759
P75 SI	<i>r</i> = -0.012 <i>P</i> = .936	<i>r</i> = 0.096 <i>P</i> = .506
P90 SI	<i>r</i> = 0.002 <i>P</i> = .988	<i>r</i> = 0.096 <i>P</i> = .505
Median SI	<i>r</i> = -0.024 <i>P</i> = .872	<i>r</i> = 0.082 <i>P</i> = .572
Mode SI	<i>r</i> = -0.017 <i>P</i> = .908	<i>r</i> = 0.023 <i>P</i> = .872
Kurtosis	<i>r</i> = -0.073 <i>P</i> = .617	<i>r</i> = 0.031 <i>P</i> = .830
Skewness	<i>r</i> = 0.297 <i>P</i> = .038	<i>r</i> = 0.261 <i>P</i> = .068
Entropy	<i>r</i> = 0.314 <i>P</i> = .028	<i>r</i> = 0.732 <i>P</i> < .001
Lesion volume	<i>r</i> = 0.473 <i>P</i> = .001	–

Significant results are given in bold.

Pearson’s correlation coefficient was used to investigate the association between SI_{mean}, SI_{min}, SI_{max}, SI_{p10}, SI_{p25}, SI_{p75}, SI_{p90}, SI_{modus}, SI_{median}, entropy, kurtosis, skewness, and tumor volume. Spearman-Rho rank-order correlation was calculated to investigate the association between SI_{mean}, SI_{min}, SI_{max}, SI_{p10}, SI_{p25}, SI_{p75}, SI_{p90}, SI_{modus}, SI_{median}, entropy, kurtosis, skewness, tumor volume, and Ki-67. Significant correlations (*P* < .05) were identified between Ki-67 and the two SI histogram parameters skewness and entropy, between entropy and tumor volume, as well as between tumor volume and Ki-67. The complete results of the correlative analysis are summarized in Table 3. Figure 2C shows a scatter plot graphically demonstrating the association of entropy and tumor volume, the set of parameters with the strongest correlation (*r* = 0.732, *P* < .001).

Discussion

To the best of our knowledge, this is the first study using a whole-tumor histogram approach to investigate T1-weighted gadolinium-enhanced images in meningiomas.

As excellently summarized by Just and coworkers [14], histogram analysis provides first-order characteristics which describe the manifestation of a specific feature (in our case, signal intensity) by means of simple descriptive statistics like mean, mode, median, minimum, maximum, and percentiles. Furthermore, second-order characteristics—skewness, kurtosis, and entropy—are also provided. These three dimensions reflect the shape of the signal intensity distribution of the investigated volume and thus provide more elaborate insight into the imaging architecture of an investigated lesion.

As expected, in accordance with previously published data, first-order characteristics of SI of postcontrast T1w MRI were not significantly different in our collective when comparing low-grade with high-grade meningiomas [11]. However, in contrast to all first-order characteristics, two items of second-order characteristics—entropy and skewness—showed an interesting trend towards distinction, albeit the conventional significance level of *P* = .05 was not achieved. We thereupon hypothesize that differences in second-order characteristics between both groups are certainly existent but subtle, and therefore, greater cohorts are necessary to achieve statistical significance.

This assumption is corroborated by the fact that both skewness and entropy showed significant correlations with expression of Ki-67. The nuclear protein is only expressed by actively proliferating cells and has been demonstrated to be a valuable molecular marker for differentiation between low-grade and high-grade meningiomas and estimation of tumor recurrence risk [22].

Also, entropy correlated significantly with tumor volume, which understandably is closely linked to tumor aggressiveness and was reported to be a strong predictor of high-grade meningiomas in cross-sectional imaging features [23].

The strongest imaging-histology correlation in our collective was found between Ki-67 labeling index and entropy. The entropy of an image is a parameter describing the degree of randomness of the respective dimension within this image. It has been used as an imaging biomarker for tumor heterogeneity in previous reports on different tumor entities [16, 24, 25]. Concerning histogram profiling of

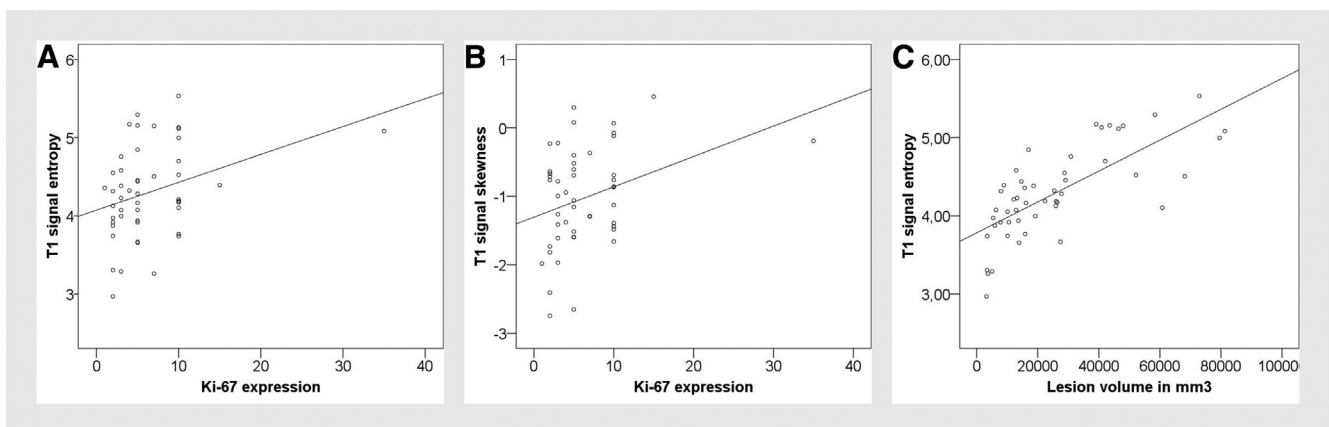


Figure 2. Scatter plots showing significant correlation between entropy and Ki-67 expression (A), between skewness and Ki-67 expression (B), and between entropy and tumor volume (C).

diffusion-weighted MRI, a more functional technique investigating the mobility of protons in biological tissues, entropy was shown to be capable of differentiating between different tumor grades [26] and further on to be significantly correlated with Ki-67 labeling index [18].

However, most previous studies examined histograms of diffusion-weighted imaging, but data for SI histograms of conventional MRI are sparse.

Only one recent study by Meyer and coworkers employed histogram analysis on conventional MRI of primary central nervous system lymphomas and reported significant imaging-histology correlations [20]. These results are in line with our presented data and encourage our hypothesis that second-order histogram parameters of simple MRI imaging data reflect certain histopathological changes and thus provide additional valuable insight into tumor biology.

More specifically, considering the results of the aforementioned studies, we take our findings as a strong indication that second-order characteristics like skewness and entropy of simple SI histograms can reflect histopathological changes, which accompany higher proliferation rates (Ki-67) and increased tumor volumes, and thus are subsidiary imaging biomarkers for tumor grade and overall prognosis, complementing the role of advanced diffusion-weighted imaging techniques.

There are some limitations of our study. First of all, it is a single-center retrospective design and based on a relative small cohort of patients. Another limitation is that only data from 1.5-T MRI systems were available, and further investigations using a 3.0-T MRI device with a higher spatial resolution would be beneficial for validation of the present results. Moreover, only postcontrast T1-weighted images were analyzed, and additional studies investigating histograms of other morphological MRI sequences, like T2-weighted images, should be undertaken.

Conclusions

Pretherapeutic histogram analysis of common morphological MRI sequences like postcontrast T1-weighted images has the potential of predicting growth kinetics and therefore estimating prognosis in the case of meningiomas.

References

- Ostrom QT, Gittleman H, Xu J, Kromer C, Wolinsky Y, and Kruchko C, et al (2016). CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2009-2013. *Neuro-Oncology* **18**, v1-v75.
- Louis DN, Perry A, Reifenberger G, Deimling von A, Figarella-Branger D, and Cavenee WK, et al (2016). The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*, 131. Berlin Heidelberg: Springer; 2016. p. 803-820.
- Claus EB, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M, and Black PM (2005). Epidemiology of intracranial meningioma. *Neurosurgery* **57**, 1088-1095 [discussion1088-95].
- Kshetry VR, Ostrom QT, Kruchko C, Al-Mefty O, Barnett GH, and Barnholtz-Sloan JS (2015). Descriptive epidemiology of World Health Organization grades II and III intracranial meningiomas in the United States. *Neuro-Oncology* **17**, 1166-1173.
- Böker DK, Meurer H, and Gullotta F (1985). Recurring intracranial meningiomas. Evaluation of some factors predisposing for tumor recurrence. *J Neurosurg Sci* **29**, 11-17.
- Marosi C, Hassler M, Roessler K, Reni M, Sant M, and Mazza E, et al (2008). Meningioma. *Crit Rev Oncol Hematol* **67**, 153-171.
- Goldbrunner R, Minniti G, Preusser M, Jenkinson MD, Sallabanda K, and Houdart E, et al (2016). EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol* **17**, e383-e391.
- Black P, Kathiresan S, and Chung W (1998). Meningioma surgery in the elderly: a case-control study assessing morbidity and mortality. *Acta Neurochir* **140**, 1013-1016 [discussion1016-7].
- Kawahara Y, Nakada M, Hayashi Y, Kai Y, Hayashi Y, and Uchiyama N, et al (2012). Prediction of high-grade meningioma by preoperative MRI assessment. *J Neurooncol*, 4 ed., 108. Springer US; 2012. p. 147-152.
- Lin B-J, Chou K-N, Kao H-W, Lin C, Tsai W-C, and Feng S-W, et al (2014). Correlation between magnetic resonance imaging grading and pathological grading in meningioma. *J Neurosurg*, 121. American Association of Neurological Surgeons; 2014. p. 1201-1208.
- Schob S, Frydrychowicz C, Gawlitza M, Bure L, Preuß M, and Hoffmann K-T, et al (2016). Signal intensities in preoperative MRI do not reflect proliferative activity in meningioma. *Transl Oncol* **9**, 274-279.
- Schob S, Meyer J, Gawlitza M, Frydrychowicz C, Müller W, and Preuß M, et al (2016). Diffusion-weighted MRI reflects proliferative activity in primary CNS lymphoma. In: Coles JA, editor. *PLoS ONE*, 11; 2016. p. e0161386.
- Woo S, Cho JY, Kim SY, and Kim SH (2014). Histogram analysis of apparent diffusion coefficient map of diffusion-weighted MRI in endometrial cancer: a preliminary correlation study with histological grade. *Acta Radiol*, 55. London, England: SAGE PublicationsSage UK; 2014. p. 1270-1277.
- Surov A, Gottschling S, Mawrin C, Prell J, Spielmann RP, and Wienke A, et al (2015). Diffusion-weighted imaging in meningioma: prediction of tumor grade and association with histopathological parameters. *Transl Oncol* **8**, 517-523.
- Schob S, Meyer HJ, Dieckow J, Pervinder B, Pazaitis N, and Höhn A-K, et al (2017). Histogram analysis of diffusion weighted imaging at 3T is useful for prediction of lymphatic metastatic spread, proliferative activity, and cellularity in thyroid cancer. *Int J Mol Sci*, 18. Multidisciplinary Digital Publishing Institute; 2017. p. 821.
- Schob S, Meyer HJ, Pazaitis N, Schramm D, Bremicker K, and Exner M, et al (2017). ADC histogram analysis of cervical cancer aids detecting lymphatic metastases—a preliminary study. *Mol Imaging Biol* **19**, 953-962.
- Surov A, Meyer HJ, and Wienke A (2017). Correlation between apparent diffusion coefficient (ADC) and cellularity is different in several tumors: a meta-analysis. *Oncotarget* **8**, 59492-59499.
- Gühr GA, Horvath-Rizea D, Garnov N, Kohlhof-Meinecke P, Ganslandt O, and Henkes H, et al (2018). Diffusion profiling via a histogram approach distinguishes low-grade from high-grade meningiomas, can reflect the respective proliferative potential and progesterone receptor status. *Mol Imaging Biol*, 18. Springer US; 2018. p. v1-v9.
- Horvath-Rizea D, Surov A, Hoffmann K-T, Garnov N, Vörkel C, and Kohlhof-Meinecke P, et al (2018). The value of whole lesion ADC histogram profiling to differentiate between morphologically indistinguishable ring enhancing lesions—comparison of glioblastomas and brain abscesses. *OncotargetImpact Journals*; 2018. p. 5.
- Meyer HJ, Schob S, Münch B, Frydrychowicz C, Garnov N, and Quäsling U, et al (2017). Histogram analysis of T1-weighted, T2-weighted, and postcontrast T1-weighted images in primary CNS lymphoma: correlations with histopathological findings—a preliminary study. *Mol Imaging Biol*, 113. Springer US; 2017 1-6.
- Surov A, Caysa H, Wienke A, Spielmann RP, and Fiedler E (2015). Correlation between different ADC fractions, cell count, Ki-67, total nucleic areas and average nucleic areas in meningotheial meningiomas. *Anticancer Res* **35**, 6841-6846.
- Abry E, Thomassen IØ, Salvesen ØO, and Torp SH (2010). The significance of Ki-67/MIB-1 labeling index in human meningiomas: a literature study. *Pathol Res Pract* **206**, 810-815.
- Hale AT, Wang L, Strother MK, and Chambless LB (2018). Differentiating meningioma grade by imaging features on magnetic resonance imaging. *J Clin Neurosci* **48**, 71-75.
- Suo S, Zhang K, Cao M, Suo X, Hua J, and Geng X, et al (2016). Characterization of breast masses as benign or malignant at 3.0T MRI with whole-lesion histogram analysis of the apparent diffusion coefficient. *J Magn Reson Imaging* **43**, 894-902.
- Foroutan P, Krehling JM, Morse DL, Grove O, Lloyd MC, and Reed D, et al (2013). Diffusion MRI and novel texture analysis in osteosarcoma xenotransplants predicts response to anti-checkpoint therapy. In: Chen X, editor. *PLoS ONE*, 8; 2013. p. e82875.
- Ryu YJ, Choi SH, Park SJ, Yun TJ, Kim J-H, and Sohn C-H (2014). Glioma: application of whole-tumor texture analysis of diffusion-weighted imaging for the evaluation of tumor heterogeneity. In: Hess CP, editor. *PLoS ONE*, 9; 2014. p. e108335.