Signal Intensities in Preoperative MRI Do Not Reflect Proliferative Activity in Meningioma

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Abstract

BACKGROUND: Identification of high-grade meningiomas in preoperative magnetic resonance imaging (MRI) is important for optimized surgical strategy and best possible resection. Numerous studies investigated subjectively determined morphological features as predictors of tumor biology in meningiomas. The aim of this study was to identify the predictive value of more reliable, quantitatively measured signal intensities in MRI for differentiation of high- and low-grade meningiomas and identification of meningiomas with high proliferation rates, respectively. *PATIENTS AND METHODS:* Sixty-six patients (56 World Health Organization [WHO] grade I, 9 WHO grade II, and 1 WHO grade I) were included in the study. Preoperative MRI signal intensities (fluid-attenuated inversion recovery [FLAIR], T1 precontrast, and T1 postcontrast as genuine and normalized values) were correlated with Ki-67 expression in tissue sections of resected meningiomas. Differences between the groups (analysis of variance) and Spearman rho correlation were computed using SPSS 22. *RESULTS:* Mean values of genuine signal intensities of meningiomas in FLAIR, T1 native, and T1 postcontrast were 323.9 ± 59, 332.8 ± 67.9, and 768.5 ± 165.3. Mean values of normalized (to the contralateral white matter) signal intensities of meningiomas in FLAIR, T1 native, and T1 postcontrast were 1.5 ± 0.3, 0.8 ± 0.1, and 1.9 ± 0.4. There was no significant correlation between MRI signal intensities and WHO grade or Ki-67 expression. Signal intensities did not differ significantly between WHO grade I and II/III meningiomas. Ki-67 expression was significantly increased in high-grade meningiomas compared with low-grade meningiomas ($P < 0.01$). Objectively measured values of MRI signal intensities (FLAIR, T1 precontrast, and T1 postcontrast enhancement) did not distinguish between high-grade and low-grade meningiomas. Furthermore, there was no association between MRI signal intensities and Ki-67 expression representing proliferative activity.

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Meningiomas are among the most common brain tumors. Their incidence is about 1%, and they account for almost one third of all primary intracranial masses. The majority of meningiomas are very slowly growing and nonsymptomatic or minimally symptomatic entities, discovered as incidental findings on neuroimaging [1]. The World Health Organization (WHO) classification system distinguishes 3 histological grades and 15 subtypes and is a well-accepted tool for prediction of prognosis. Although most meningiomas are benign masses, certain histological subtypes reveal very high recurrence rates despite the tumors' seemingly total removal. Grade II (atypical) and grade III (anaplastic) meningiomas are associated

with an increased risk of recurrence, are more aggressive, and show invasive behavior [2]. Grade I meningiomas are generally considered

as benign tumors, but recent studies indicate substantial neurological deficits and impaired long-term survival due to tumor recurrence and stroke despite their low histopathological grading in a considerable proportion of cases [3,4]. Increased mitotic activity (more than 4 mitoses per 10 high-power fields) and elevated Ki-67 expression (Ki-67 index of more than 5% of nuclei) are reliable histopathological markers for tumor recurrence [2].

Because histopathological grading alone does not predict outcome satisfyingly, numerous studies investigated the value of preoperative magnetic resonance imaging (MRI) for prognostics. For example, Liu et al. demonstrated that hyperintensity on diffusion-weighted imaging, heterogeneous gadolinium enhancement, disruption of the arachnoid at brain tumor interface, T2 hyperintense peritumoral edema, and irregular tumor shape were independent predictors of non–grade I meningioma [5]. Other works produced comparable results, although some of these studies underline the importance of positive capsular enhancement [6,7], whereas others emphasize the predictive value of peritumoral edema [5,8]. All the above-cited works investigated morphological features of meningiomas summarized in subjective scoring systems, but not one of the studies objectively analyzed values of SIs in commonly used preoperative MRI sequences.

Therefore, the aim of this study was to investigate the predictive value of genuine and normalized SIs of standardized preoperative MRI (T1 pre- and postcontrast, T2, and fluid-attenuated inversion recovery [FLAIR]) as *in vivo* predictors of proliferative activity of meningiomas.

Material and Methods

This study was approved by the institutional review board (Martin Luther University Ethics Committee).

Patients

Overall, 66 patients with different meningiomas were included into the retrospective analysis. There were 50 women and 16 men with a mean age of 59.7 ± 15.8 years. In 56 patients (approximately 84.8%), WHO grade I tumors were diagnosed. Most frequently, meningothelial meningiomas ($n = 32$,) followed by transitional ($n = 12$), fibroblastic ($n = 7$), angiomatous ($n = 4$), and psammomatous ($n = 1$) subtypes were identified. Grade II tumors were identified in 9 cases (13.6%) and grade III in 1 (1.5%).

MRI

In all patients, cranial MRI was performed using a 1.5-T device (Magnetom Vision Sonata Upgrade, Siemens, Erlangen, Germany). The imaging protocol included the following sequences:

1. Axial T2-weighted (T2w) fluid-attenuated inversion recovery (FLAIR) sequence (repetition time/echo time: 8000/129, slice thickness: 5 mm, acquisition matrix: 256 × 256, field of view: 230 mm);
2. Axial and coronal T1-weighted (T1w) spin echo sequences (repetition time/echo time: 562/16, slice thickness: 5 mm, acquisition matrix: 256 × 256, field of view: 230 mm) before and after intravenous application of contrast medium (gadopentate dimeglumine, Magnevist, Bayer Schering Pharma, Leverkusen, Germany).

All images were available in digital form and were analyzed by one radiologist (A. S., 14 years of radiological experience) on a PACS workstation (Centricity PACS, GE Medical Systems, Milwaukee, WI).

The slices with the largest diameter of each tumor were selected for signal intensity (SI) calculation. In every case, a polygonal region of interest (ROI) as large as possible was manually drawn on postcontrast T1w images. Every ROI was automatically placed also on all other images (T2w and precontrast T1w). Cystic and necrotic areas as well as large vessels of the tumors were not considered for evaluation. In all images, mean SI values were estimated. Furthermore, ROIs were drawn in the normal white matter of the contralateral hemisphere (SI white matter). Normalized SI was calculated in every case as the ratio SI meningioma/SI white matter. In addition, for each lesion, the ratio SI on postcontrast T1w/SI on precontrast T1w was calculated (SI contrast). Figures 1 and 2, *a–c*, exemplarily show axial images (FLAIR, T1 precontrast, T1 postcontrast) of WHO grade I (transitional) and WHO grade II (atypical) meningiomas.

Histopathology and Immunohistochemistry

All included meningiomas were surgically resected and histopathologically analyzed. Tumor grading was classified according to the WHO [2].

In every case, the proliferation index was estimated on Ki-67 antigen-stained specimens by using MIB-1 monoclonal antibody (DakoCytomation, Denmark) as reported previously [9]. Two high-power fields (0.16 mm^2 per field, ×400) were analyzed. The area with the highest number of positive tumor nuclei was selected. Figures 1*d* and 2*d* exemplarily show Ki-67 immunostaining of WHO grade I (transitional) and WHO grade II (atypical) meningiomas.

Statistical Analysis

Statistical analysis was performed using SPSS Version 22. Differences between groups were assessed using one-way analysis of variance. Correlations between Ki-67 expression and genuine or normalized SIs, respectively, were calculated using a Spearman rho correlation. Significance level was set to .05.

Results

MR SIs (T1 precontrast, FLAIR, T1 postcontrast, and normalized SIs) of the investigated grade I to III meningiomas and Ki-67 expression (%) are shown in Table 1.

One-way analysis of variance did not show significant differences between meningiomas of WHO grade I, II, or III regarding their MRI SIs. The difference in Ki-67 expression achieved statistical significance ($P < .01$) between low-grade and high-grade meningiomas. Figure 3, *a–h*, summarize the relation of MRI SIs and Ki-67 expression between WHO grade I and WHO grade II/III meningiomas. For reasons of simplicity and clarity, high-grade meningiomas (grade II and III meningiomas) are displayed together and compared with grade I meningiomas.

No correlation was found between MRI SIs and Ki-67 expression. Table 2 displays results of statistical analysis of the correlation between SIs (genuine and normalized) and Ki-67 expression.

Discussion

We investigated in meningiomas the relationship between objectively measurable SIs on standard preoperative MRI and the proliferative activity in histopathology. Expression of the proliferation associated antigen Ki-67 was significantly higher in grade II and III meningiomas, but there was neither a significant difference of MRI SIs among grade I, II, or III meningiomas nor a correlation between Ki-67 expression and MRI SIs.

Preoperative MRI is a valuable tool for identification and follow-up of meningiomas with aggressive behavior in the clinical routine. High-grade meningiomas are a significant cause of morbidity and mortality and need to be identified prior to surgery to achieve the best resection. Numerous studies investigated morphological
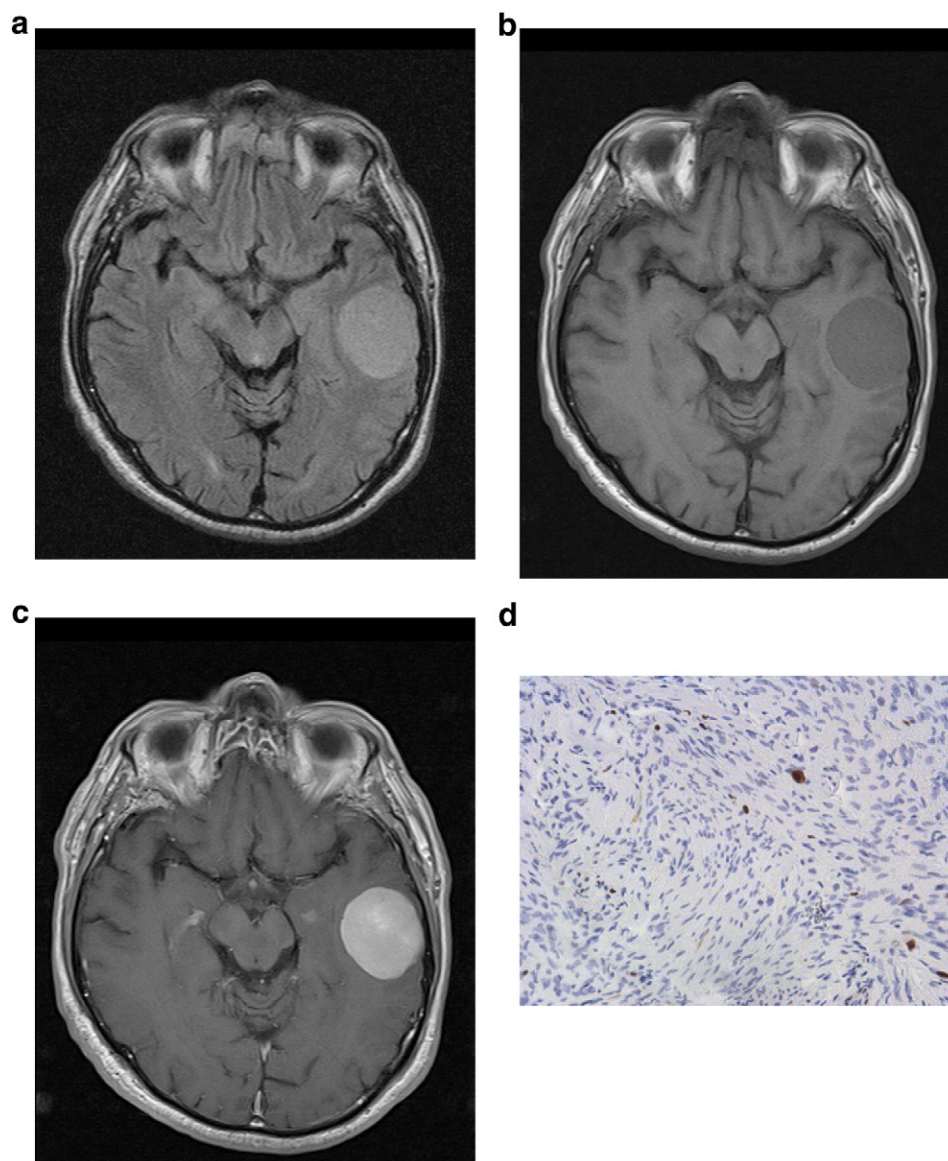
Figure 1. (a–d) Imaging findings (FLAIR, T1 precontrast, T1 postcontrast) and Ki-67 staining of a WHO grade I meningioma. Signal intensities were as follows: normalized FLAIR SI = 1.47, normalized precontrast T1 SI = 0.81, normalized postcontrast SI = 1.77, and postcontrast SI/precontrast SI = 2.24. Ki-67 index = 3%.

features of meningiomas in MRI to identify *in vivo* attributes that predict invasiveness and increased risk of recurrence [5–8,10,11]. Consensually, peritumoral edema, ill-defined tumor margins, heterogeneous contrast enhancement, and absence of a subarachnoidal rim surrounding the tumor are important indicators of non–grade I meningiomas with aggressive tumor growth, high recurrence risk, and a tendency of infiltration of surrounding parenchyma. Nevertheless, these are subjective criteria only describing morphological features. Interobserver and intraobserver variability significantly reduces the reliability of these prediction models [6]. Previously, few studies investigated imaging parameters semiquantitatively and their relationship to histopathological features with at least partially contradictory findings. In earlier years Maiuri and coworkers [12] analyzed T1 and T2 SIs (clinically applied as categories of hypointensity, isointensity, and hyperintensity) in meningiomas and found that T1w images may predict the presence of cysts and intratumoral blood vessels, whereas T2w images may be able to give information about histological subtype, vascularity, and consistency. More recently, Hadidy and colleagues examined the association between SI on T1w and T2w FLAIR MRI (with very approximate categories of hypointensity, isointensity, and hyperintensity) as well as contrast enhancement patterns and histopathological grading [13] and found no correlation between MRI and histopathology. Besides these studies, other authors investigated the association between cellularity, Ki-67 expression, and different apparent diffusion coefficient fractions in low-grade and high-grade meningiomas and were able to show that apparent diffusion coefficient mean is able to distinguish between grade I and grade II/III meningiomas [14]. To the best of our knowledge, no further studies exist that investigated the correlation between objectively measurable, numeric MRI SIs and histopathological features, especially Ki-67 expression representing proliferative activity.

This study clarifies that even numerically quantified SIs of meningiomas in preoperative MRI cannot distinguish between low-grade, noninvasive meningiomas and high-grade, aggressive-invasive meningiomas.
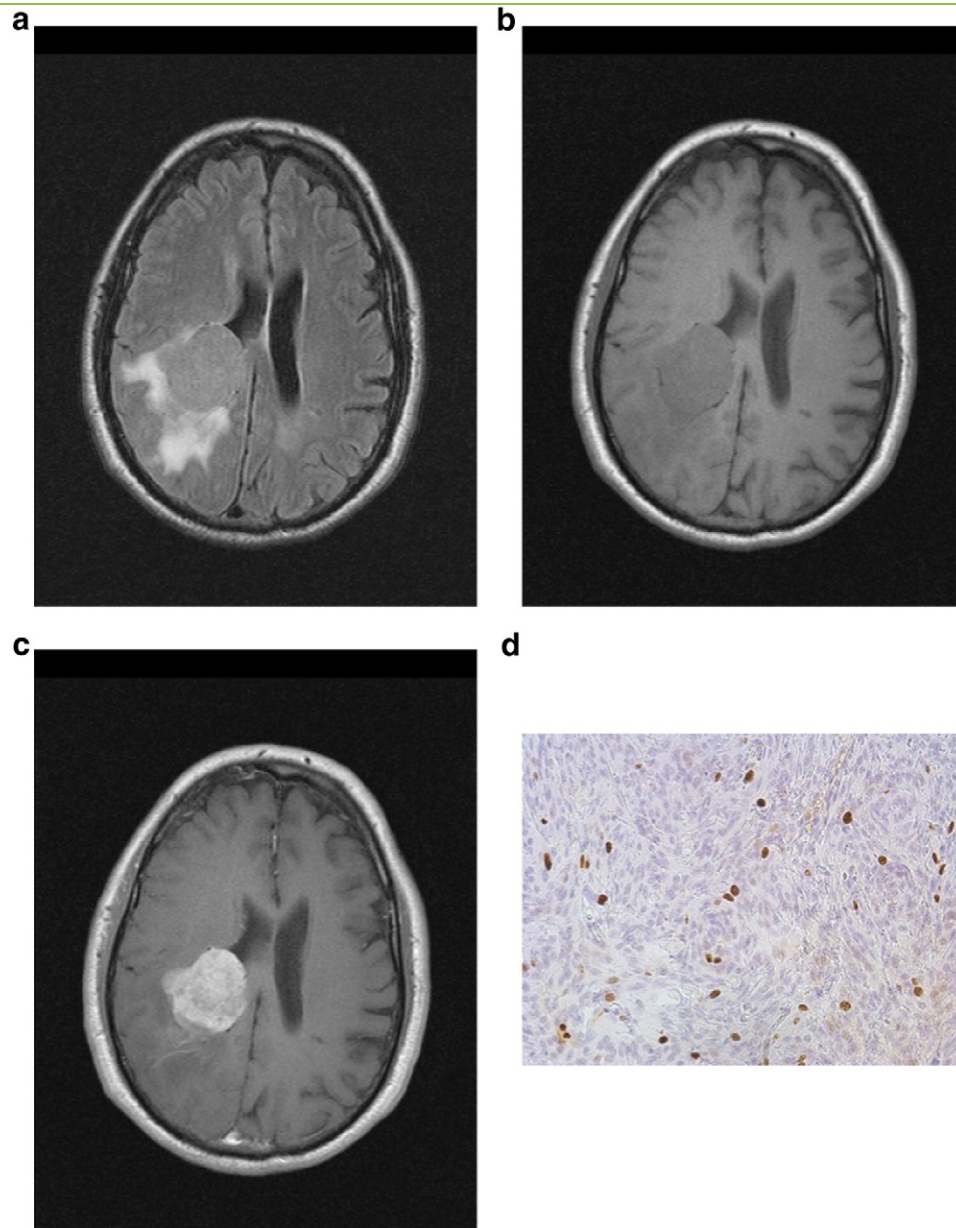
Figure 2. (a–d) Imaging findings (FLAIR, T1precontrast, T1 postcontrast) and Ki-67 staining of a WHO grade II (atypical) meningioma. Signal intensities were as follows: normalized FLAIR SI = 1.45, normalized T1 precontrast SI = 0.87, normalized postcontrast SI = 1.88, and postcontrast SI/precontrast SI = 1.97. Ki-67 index = 18%.

Table 1. MRI SIs Displayed as Genuine and Normalized Values (SI of the Respective Meningioma, m', Divided by the SI of the Unaffected Contralateral White Matter ,wm') and Ki-67 Expression of All Investigated Meningiomas

	Mean ± SD	Median	Range
T1 meningioma	332.8 ± 67.9	324	197-500
T1 white matter	407.2 ± 63.5	411	276-600
T1 m/wm	0.8 ± 0.1	0.8	0.6-1.0
FLAIR meningioma	323.9 ± 59	317	200-495
FLAIR white matter	211.5 ± 26.8	210	145-285
FLAIR m/wm	1.5 ± 0.3	1.5	1.0-2.5
T1 postcontrast meningioma	768.5 ± 165.3	764	512-1300
T1 postcontrast white matter	407.7 ± 67.6	413.5	256-630
T1 pos contrast m/wm	1.9 ± 0.4	1.9	1.1-2.9
T1 postcontrast m/wm T1 native m/wm	2.3 ± 0.4	2.3	1.7-3.5
Ki-67 expression %	5.2 ± 5.3	3	1-20

Our work suffers some limitations. Firstly, it is of retrospective nature, and secondly, the number of analyzed high-grade meningiomas is comparatively small.

Conclusion

To optimize surgical therapy, it is necessary to identify aggressive and invasive meningiomas on preoperative MRI. Numerous subjective scoring systems have been developed on the basis of morphological features of meningiomas in MRI to separate high-grade from low-grade meningiomas with varying sensitivities. This is the first study that investigated the value of objectively measured, quantified SIs as predictors of aggressive tumor behavior. Counterintuitively, quantitatively measured SIs of standardized preoperative MRI were not able to differentiate low -from high-grade meningiomas or to identify meningiomas with a high proliferative activity.
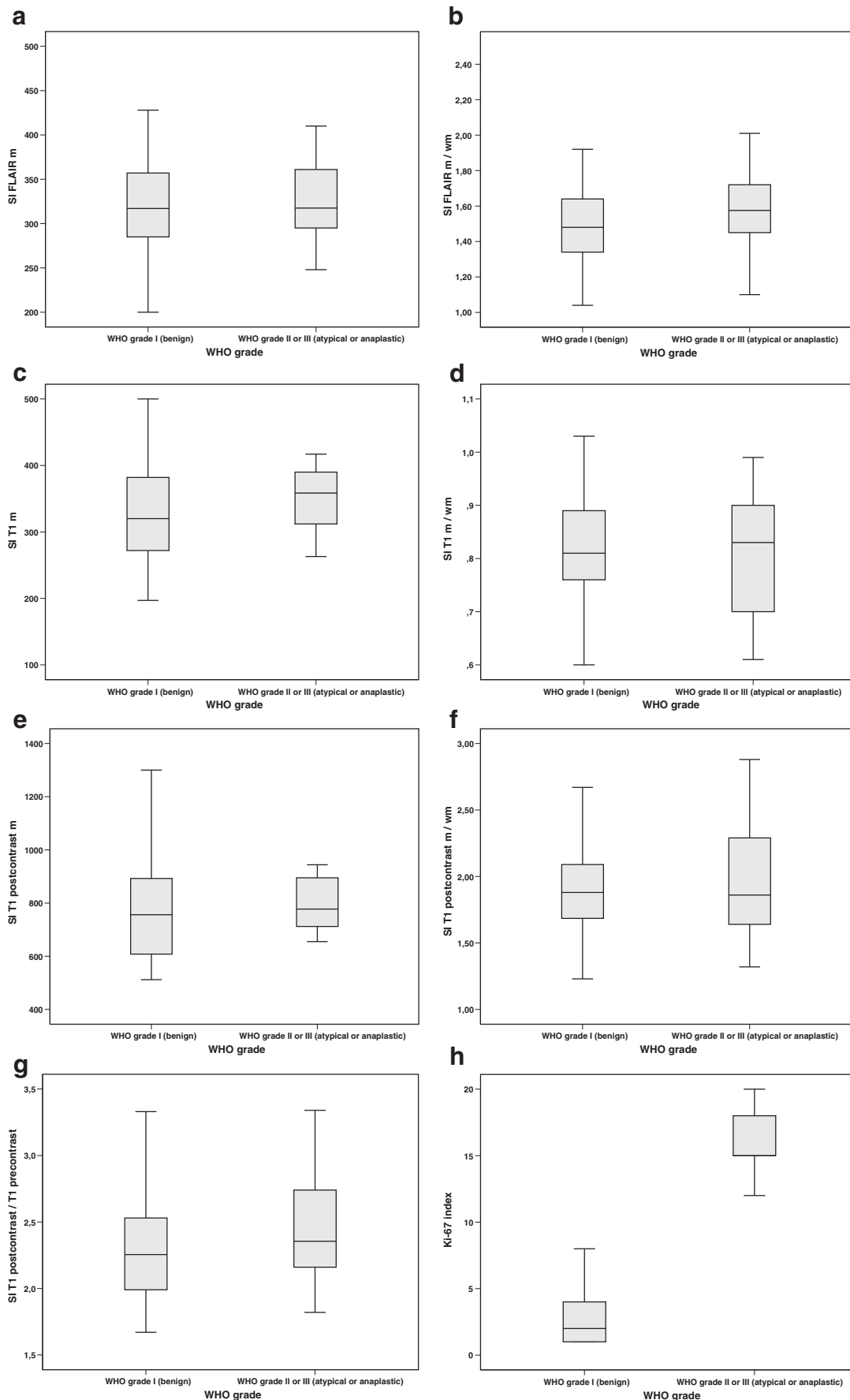
Figure 3. (a–h) Box plots give an overview on the relation of MRI SI (a–g) and Ki-67 index between low-grade and high-grade meningiomas.

Table 2. Statistical Correlations between Genuine and Normalized SIs of Meningioma and Ki-67 Expression

	T1 m	T 1 m/wm	FLAIR m	FLAIR m/wm	T1 pc m	T1 pc m/wm	T1 pc/T1 native
Ki-67 %	$r = -0.9$	$r = -0.186$	$r = -0.48$	$r = 0.002$	$r = -0.99$	$r = -0.109$	$r = 0.029$
	$P = -.489$	$P = .152$	$P = .723$	$P = .991$	$P = .439$	$P = .396$	$P = .827$

There are no conflicts of interest.

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