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ORIGINAL RESEARCH

Low-Field MR Imaging of Meningiomas Including Dynamic Contrast Enhancement Study: Evaluation of Surgical and Histopathologic Characteristics

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BACKGROUND AND PURPOSE: Risks associated with surgery of meningiomas, especially those located in the skull base, are influenced by tumor consistency and vascularity. The purpose of this study was to find out if vascularity, consistency, and histologic characteristics of meningioma can be predicted preoperatively by using low-field MR imaging, including dynamic imaging of contrast enhancement.

MATERIALS AND METHODS: Twenty-one patients (mean age, 56; range, 34–73 years; 16 women, 5 men) with meningioma requiring first surgery were imaged by a 0.23T scanner. Time to maximum enhancement, maximum enhancement, and maximum intensity increase were noted from the enhancement curve of dynamic imaging. Relative intensity of tumor in fluid-attenuated inversion recovery (FLAIR) and T2-weighted images was calculated. The neurosurgeon evaluated surgical bleeding and hardness of tumor on a visual analog scale. Histopathologic analysis included subtype, World Health Organization grade, mitotic activity, grades of progesterone receptor expression and collagen content, proliferation activity by Ki-67 (MIB-1), and microvessel density by CD34. Correlations were studied with Kendall τ statistics.

RESULTS: The most powerful association was found between time to maximum enhancement and microvessel density ($\tau = -0.60$, $P < .001$). Surgical bleeding ($\tau = 0.49$, $P = .002$), blood loss during surgery ($\tau = 0.49$, $P = .002$), progesterone receptor expression ($\tau = 0.59$, $P < .001$), and collagen content ($\tau = -0.54$, $P < .001$) were statistically best correlated with the relative intensity of meningioma on FLAIR images. Tissue hardness correlated best with relative intensity on T2-weighted images ($\tau = 0.40$, $P = .012$).

CONCLUSION: Assessment of microvessel density, collagen content, and progesterone receptor expression of meningioma may be clinically feasible by using low-field MR imaging.

Preoperative estimates of vasculature, consistency, and histopathologic features of meningiomas would be valuable aids in surgical planning, especially in cases in which the tumor is located in the skull base or in which it encases cranial nerves or important blood vessels.[1-4] Correlation between hyperintensity of meningioma in T2-weighted imaging and tissue softness as well as increased vascularity has been found at 1.5T.[5-7] Hyperintensity in proton attenuation images has also been found to correlate with soft tumors.[6,7] Meningioma subtype may affect intensity on T2-weighted images.[5,6] However, statistically significant correlations have not been shown in all studies.[8] Yoneoka et al[9] found that intensity heterogeneity on T2-weighted imaging correlated with hard tumors at 3T field strength. According to these previous studies, signal intensity of meningiomas on unenhanced T1-weighted images does not correlate with tumor consistency, vascularity, or histologic findings[5-8] nor does the degree of contrast enhancement correlate with these factors.[5]

Instant repetitive T1-weighted imaging after injection of gadopentenate dimeglumine (Gd-DTPA, Magnevist, Schering AG, Berlin, Germany) reveals characteristics of the enhancement dynamics. The up-slope of a dynamic enhancement curve is highly dependent on tissue perfusion with interaction of microvessel permeability. Maximum enhancement is related to the total uptake of the contrast medium in the interstitial space, and contrast agent concentration decrease is strongly related to vascular permeability.

Dynamic T1-weighted imaging has been found to be helpful in differentiating extra-axial intracranial tumors at 1.5T.[10-12] In addition, Ikushima et al[11] found that enhancement patterns of meningothelial and fibrous subtypes of meningiomas are different in most cases. Parameters derived from the T1 enhancement curve that represents rate of contrast accumulation have also been reported to distinguish between subjectively rated typically and atypically vascularized meningiomas at 1.5T.[13] The maximum signal intensity has been found to correlate with microvessel density, and the time-to-peak intensity has been found to correlate negatively with tissue blood flow of meningiomas.[14]

Imaging times at low-field strength tend to be longer, thus impeding dynamic imaging. Projection reconstruction imaging[15] has been used to achieve short scanning times and motion insensitivity in heart and diffusion imaging, guidance tests in low-field interventional MR imaging procedures, and contrast-enhanced MR angiography at 1.5T.[16-19]

The purpose of our study was to assess whether preoperative low-field MR imaging that includes dynamic imaging of contrast enhancement by using undersampled projection reconstructed spin-echo sequences[20] can help to predict consistency, vascularity, and histologic characteristics of meningiomas. This assessment was done by comparing imaging results, surgeons' evaluations of surgical bleeding and hardness of tissue, and histopathologic characteristics. To our knowledge,

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this is the first series studying dynamic contrast enhancement of brain tumors by using an imager of less than 0.5T.

Methods

Patient Population

Twenty-one patients with meningioma undergoing first surgery were included in this prospective study. Operations were consecutive except for those patients for whom a preoperative imaging could not be properly arranged. Patients who had undergone embolization of tumor feeding arteries were also excluded. The age range of the patient population was 34–73 years (mean age, 56 years). Sixteen patients were women, and 5 were men. Except for 1 World Health Organization (WHO) grade II tumor, all were grade I tumors. Informed consent was obtained from the patients.

Imaging Protocol

MR imaging was performed in an intraoperative MR imaging unit[21] with an open 0.23T imager (Philips Medical Systems MR Technologies Finland, Vantaa, Finland). The MR imaging examination began with the acquisition of anatomic images of the whole brain by using fast spin-echo sequences, nonenhanced T1-weighted images (TR, 500 ms; TE, 16 ms; echo-train length [ETL], 2) in the sagittal plane, and T2-weighted images (TR, 4500 ms; TE, 120 ms; ETL, 16) in the axial plane with section thickness of 5 mm and FOV of 250 × 250 (matrix 256 × 256). In addition, the fluid-attenuated inversion recovery sequence (FLAIR) (TR, 5715–6249 ms; TE, 80–88 ms; TI, 2000–2200 ms; thickness, 5 mm; FOV, 211 × 250; matrix 216 × 256; ETL, 12) was performed in the axial plane. After the intravenous injection of 0.1 mmol/kg of Gd-DTPA and dynamic contrast-enhanced imaging, a T1-weighted sequence was repeated in the sagittal plane. The T1-weighted 3D field/gradient-echo sequence was performed in the axial and coronal planes (TR, 25 or 24 ms; TE, 10 or 9.0 ms; flip angle, 35°; thickness, 5 mm; FOV, 211 × 250; matrix, 324 × 384).

Dynamic T1-weighted imaging (TR, 150 ms; TE, 15 ms) was performed by using an undersampled projection-reconstructed sequence with 42 projections $[0, \pi[$. A precontrast image frame was obtained after which the contrast agent bolus was injected into the antecubital vein at a rate of 3 mL/s immediately followed by a 20-mL saline flush. Repetitive scanning of dynamic imaging frames was initiated simultaneously with the start of contrast agent injection, and the sequence was then repeated 30 times. Frames were scanned every 7.3 seconds for the first 7 patients and every 6.8 seconds for the remainder of the patients because of imager software upgrade. Thus, the contrast enhancement was followed for 219 seconds in 7 cases and 204 seconds in 14 cases. Each frame consisted of either 6 sections (thickness, 10 mm) or, when imaged in the sagittal plane, 5 sections and a saturation slab. A more-detailed description of the sequence has been published elsewhere.[20]

Data on Tumor Tissue Characteristics

Neurosurgeons completed a form inquiring about tumor consistency and surgical bleeding as continuous variables on visual analog scales (VAS) from zero (soft and scarcely vascular) to 10 (hard and very vascular). The form also included questions on other characteristics of meningiomas and the operation, including location of tumor, occurrence of cysts, calcification, necrosis, hemorrhage, infiltration, duration of the operation, and blood loss.

In addition to meningioma subtype and WHO grade, histopathologic assessment of tissue blocks included evaluation of mitotic activity (mitoses/10 high-powered field), grade of cellularity, grade of progesterone receptor expression and grade of collagen content semiquantitatively (0–3) by van Gieson stain, proliferation activity by Ki-67 (MIB-1) marker (mean of positive nuclei/square millimeter), and microvessel density by CD34 endothelial marker (mean of stained endothelial spaces/square millimeter). Neither the surgeons nor the neuropathologist knew the results from the dynamic imaging before they assessed the tumor characteristics.

Data Analysis

Enhancement curves were drawn by using a region-of-interest tool placed over the tumor in an image in which the tumor was clearly detectable (ie, it had already enhanced). A section was selected from the middle of the tumor. A region of interest was then drawn to cover the tumor intersection and exclude borders prone to partial volume effect. The scanner software calculated the curve of mean signal intensity inside the region of interest as a function of time. The software also gave the time point (in seconds) and signal intensity (in arbitrary units) of maximum enhancement as well as the time of steepest slope. To enable comparison between patients, we divided the value of maximum intensity by the intensity value of a reference region of interest drawn on white matter. The relative hyperintensity value of tumor in the reference imaging frame was calculated similarly.

The time point of bolus arrival (steepest slope) to the venous sinuses was taken from a section in which the sagittal sinus or parasagittal cortical veins were seen and was used as reference (ie, this time point was subtracted from the time point of maximum enhancement). This procedure was done to eliminate effects caused by differences in circulation times. In the present study, this parameter is named "time to maximum enhancement." Enhancement of veins was used as a reference because these structures are more easily visible on low-field MR images of brain than are arteries. The bolus passes the normal capillary system instantly, compared with the time that contrast enhancement of meningioma takes. The relative maximum intensity value was divided by the relative reference intensity of the tumor to get a value representing maximum intensity increase. The time intensity curves were also coarsely assessed according to the curve shape.

Intensities of meningiomas were quantified on T2-weighted and FLAIR images by selecting a section that was nearest to the one used in the dynamic imaging analysis. The region of interest was drawn to the intersection of tumor. The relative intensity value was calculated by dividing tumor intensity value by the intensity of a reference region of interest drawn on cortical gray matter. Hence, tumors with values of relative intensity of under 1 were hypointense; approximately 1, isointense; and above 1, hyperintense relative to cortical gray matter.

Statistical analysis was done by using R 2.0.1 software (The R Foundation for Statistical Computing). Normality test of data was performed by using the Shapiro-Wilk test. Kendall τ correlation coefficient was used to measure association because most of the data did not come from a normal distribution. Two-tailed P values were calculated: P values greater than .05 were considered statistically not significant. This criterion was used to extract from the multitude of studied correlations the most prominent ones. τ takes values between -1 and $+1$ like other measures of correlation. Value $+1$ indicates perfect positive association and -1 perfect negative association. Zero indicates that there is no correlation between parameters.

Correlations between MRI and tissue parameters expressed by values of τ correlation coefficient

Imaging Parameter	Hardness	Surgical Bleeding	Blood Loss	Progesterone Receptors	Microvessel Density	Collagen Content
Time to maximum enhancement	NS	−0.39 ($P = .014$)	NS	NS	−0.60 ($P < .001$)	0.38 ($P = .016$)
Maximum enhancement	NS	0.39 ($P = .013$)	0.41 ($P = .009$)	0.46 ($P = .004$)	0.39 ($P = .014$)	−0.37 ($P = .020$)
Maximal intensity increase	NS	0.35 ($P = .026$)	0.39 ($P = .013$)	0.39 ($P = .014$)	0.46 ($P = .004$)	−0.32 ($P = .043$)
Relative intensity T2	−0.40 ($P = .012$)	0.44 ($P = .005$)	0.42 ($P = .008$)	0.41 ($P = .009$)	NS	−0.52 ($P = .001$)
Relative intensity FLAIR	−0.35 ($P = .028$)	0.49 ($P = .002$)	0.49 ($P = .002$)	0.59 ($P < .001$)	NS	−0.54 ($P < .001$)

Note:—FLAIR indicates fluid-attenuated inversion recovery; NS, not significant ($P > .05$).

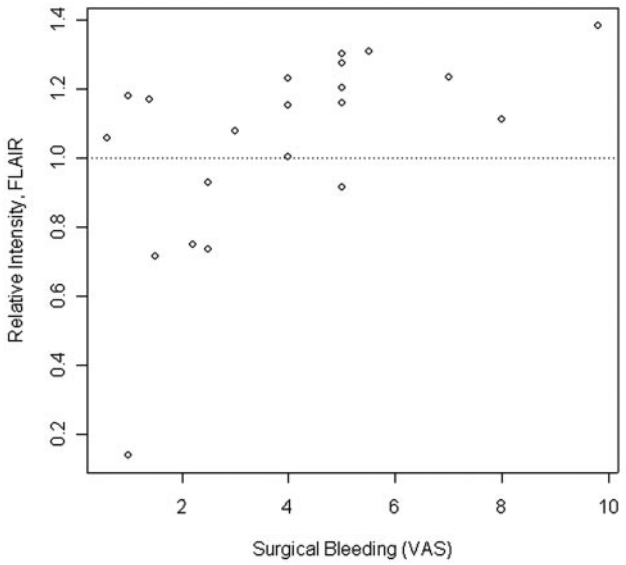

Fig 1. Relative intensity on FLAIR images versus surgical bleeding of tumor tissue evaluated on VAS ($\tau = 0.49$, $P = .002$).

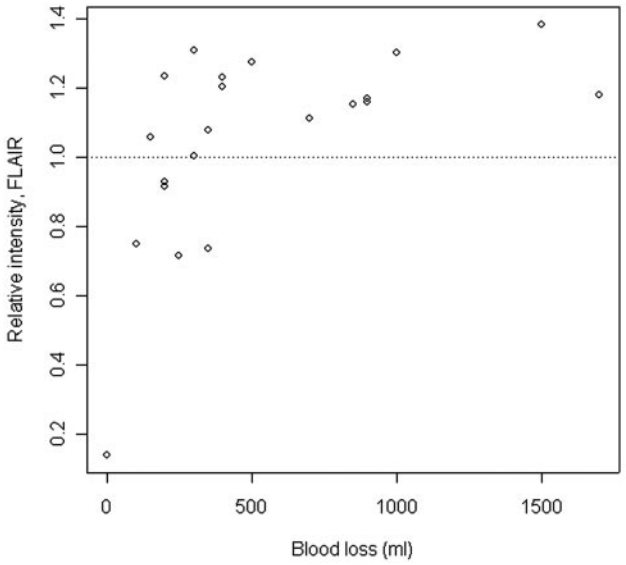

Fig 2. Relative intensity of tumor tissue on FLAIR images versus blood loss during surgery ($\tau = 0.49$, $P = .002$).

Results

The Table summarizes the correlations between imaging, operative, and histologic parameters by using Kendall τ values. No correlation was found between any dynamic imaging parameter and tissue hardness nor between time to maximum enhancement and blood loss or progesterone receptor expression. Relative intensities on T2 and FLAIR images did not correlate with microvessel density.

FLAIR and T2-Weighted Images

The Table also shows that surgical bleeding ($\tau = 0.49$, $P = .002$), blood loss ($\tau = 0.49$, $P = .002$), progesterone receptor expression ($\tau = 0.59$, $P < .001$), and amount of collagen in tumor tissue ($\tau = -0.54$, $P < .001$) correlated best with relative intensity of meningioma in FLAIR images. Figures 1–4 present these parameters for each patient. Hardness of meningiomas correlated best with relative intensity on T2-weighted images ($\tau = -0.40$, $P = .028$) (Fig 5).

The sensitivity, specificity, and positive predictive value of FLAIR intensity to predict blood loss were 1.00, 0.55, and 0.67, respectively. The limit for "disease positive" was 400 mL or more blood loss. The criterion for a positive test result was relative intensity of 1 or more. The previously mentioned statistical parameters for FLAIR intensity to predict progesterone

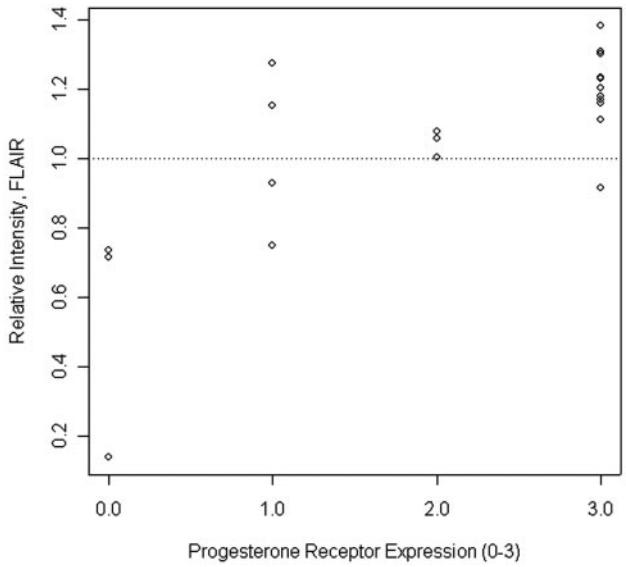

Fig 3. Relative intensity of tumor tissue on FLAIR images versus grade of progesterone receptor expression evaluated on a scale of 0–3 ($\tau = 0.59$, $P < .001$).

receptor expression were 0.93, 0.71, and 0.87, respectively. The criterion for a positive test result was as indicated previously and for a positive disease result was grades 2 and 3 of proges-

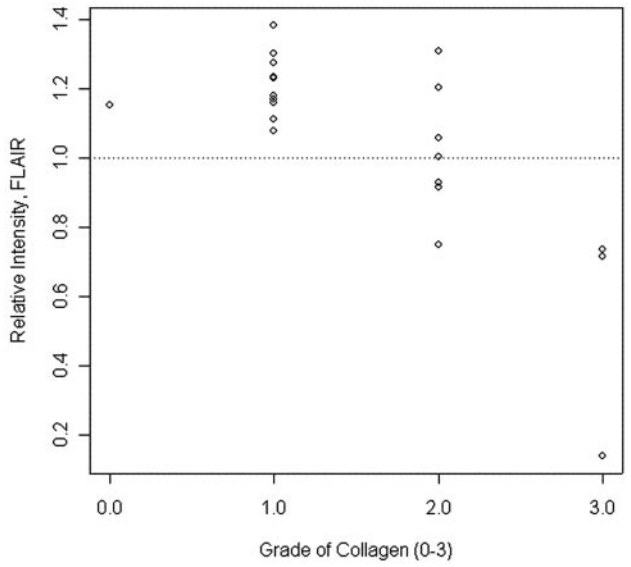

Fig 4. Relative intensity of tumor tissue on FLAIR images versus grade of collagen content evaluated on a scale of 0–3 ($\tau = -0.54$, $P < .001$).

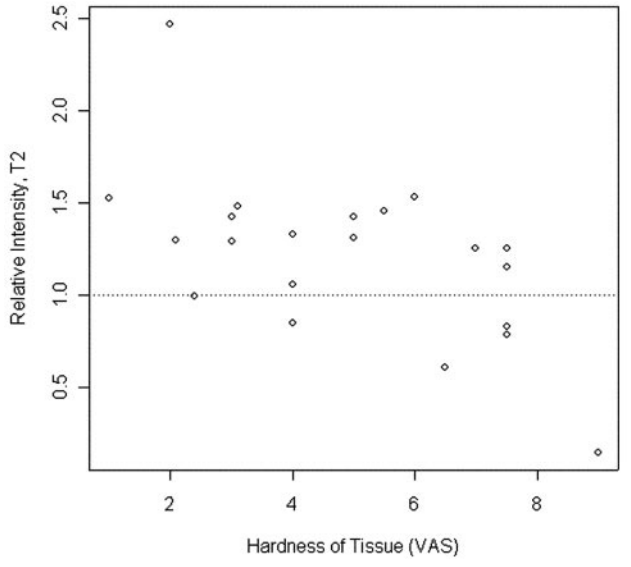

Fig 5. Relative intensity on T2-weighted images versus hardness of tumor tissue evaluated on VAS ($\tau = -0.40$, $P = .012$).

terone receptor expression. The sensitivity, specificity, and positive predictive value of FLAIR intensity to predict collagen content were 0.6, 1.0, and 1.0, respectively. Now, the positive test criterion was relative intensity less than 1 and the positive-disease-criterion collagen grades 2 and 3.

Differences in relative intensity between T2 and FLAIR images were also calculated, but this parameter did not give better correlations than did the relative intensities themselves: correlation between intensity difference and hardness, $\tau = -0.31$, $P = .051$; and correlation of intensity difference and amount of collagen, $\tau = -0.34$, $P = .030$.

Dynamic Imaging

The most powerful association found in this study ($\tau = -0.60$, $P < .001$) was between time to maximum enhancement and microvessel density. Time to maximum intensity forms a logarithmically descending curve with increasing microvessel density (Fig 6). The sensitivity, specificity, and positive predictive value for time to maximum enhancement to predict microvessel attenuation were 1.00, 0.80, and 0.85, respectively. The limit for test positive was maximum enhancement within 60 seconds and disease positive microvessel density of 100 or more microvessels/square millimeter. Thus, all 11 meningiomas having more than 100 capillaries/square millimeter and only 2 that contained fewer enhanced to maximum within 60 seconds. Mean microvessel density was 162 microvessels/square millimeter, and median was 111 microvessels/square millimeter. All 4 fibrous but only 3 of the 12 meningothelial meningiomas took more than 60 seconds to reach maximum enhancement. All 3 secretory meningiomas reached maximum enhancement within 60 seconds.

Nine of 12 meningothelial tumors and all 3 secretory tumors, but none of the 4 fibrous ones, enhanced rapidly, then gradually declined in intensity. Three meningothelial meningiomas and 1 fibrous one enhanced relatively rapidly followed by nearly constant intensities. Three of 4 fibrous meningiomas showed slow increase of intensity without a clear turning point within the imaging time period.

Sample Tumors

T2 and FLAIR images of 1 fibrous and 2 meningothelious tumors are presented in Figs 7−9. Microvessel density was counted from CD34 stained specimens, and for the sample tumors, it was 560, 151, and 81 microvessels per mean square millimeter, respectively. These tumors enhanced to maximum in 10, 22, and 90 seconds, respectively.

The studied imaging parameters were compared with each other. The strongest correlation was found between maximum intensity increase and maximum enhancement ($\tau = 0.77$, $P < .001$). Intensities in FLAIR and T2-weighted images were also highly correlated ($\tau = 0.73$, $P < .001$).

Discussion

The purpose of this study was to find out if vascularity, consistency, and histologic characteristics of meningioma can be predicted by using low-field MR imaging. Vascularity and consistency were studied by asking operating neurosurgeons for an evaluation of hardness and operative bleeding of the tumor. Histopathologic parameters, amount of collagen, and microvessel density are also related to these macroscopic characteristics. The greatest values of τ obtained in this study may be generalized to represent moderate ($0.40 < \tau > 0.60$) or strong correlations ($0.60 < \tau > 0.80$). None of studied imaging parameters seem to give correlations that could be clinically usable for prediction of hardness of tissue on the VAS scale in individual patients. The scatterplot (Fig 5) shows significant overlap of relative intensities on T2-weighted images. Scatterplots of surgical bleeding, blood loss, progesterone receptor expression, and grade of collagen versus intensity on FLAIR images showed overlap, too. Still, especially progesterone receptor expression and grade of collagen content showed clearer tendencies and point to the possibility of predicting these parameters in some cases. For example, tumor tissue that is hypointense on FLAIR images is unlikely to bleed profusely during surgery, probably resulting in minor blood loss. Hypointense tumors are also likely to have absent or relatively

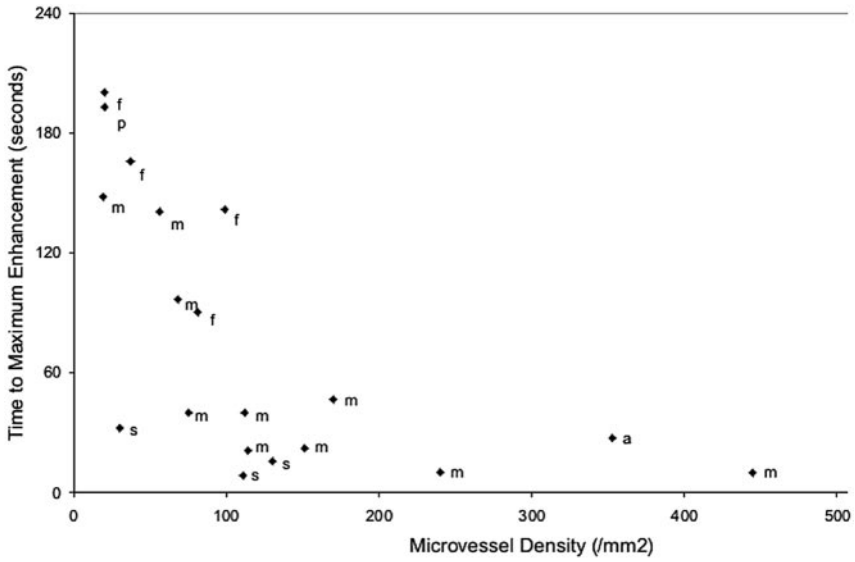

Fig 6. Time to maximum intensity on dynamic study versus microvessel density ($\tau = -0.60$, $P < .001$). m indicates meningothelial; f, fibrous; s, secretory; p, psammomatous; and a, angiomatous meningioma.

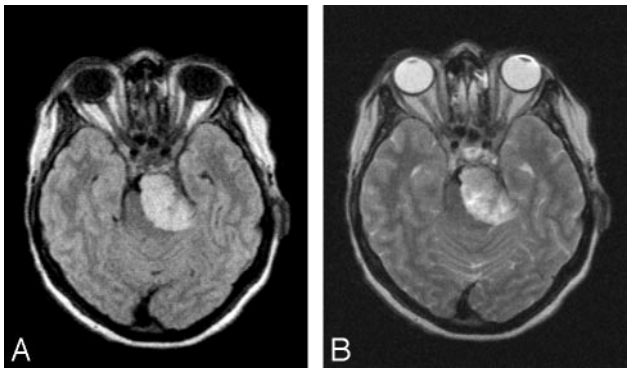

Fig 7. Meningothelial meningioma (*A*) FLAIR image (relative intensity of tumor, 1.15). *B*, T2-weighted image (relative intensity, 1.42). Surgical bleeding, grade 4 on VAS and blood loss, 850 mL; hardness 5 on VAS; collagen content, 0; progesterone receptor expression, 1; microvessel density, 560 microvessels/mm^2. Time to maximum enhancement in dynamic imaging was 10 seconds from the time point when contrast agent arrived in the veins.

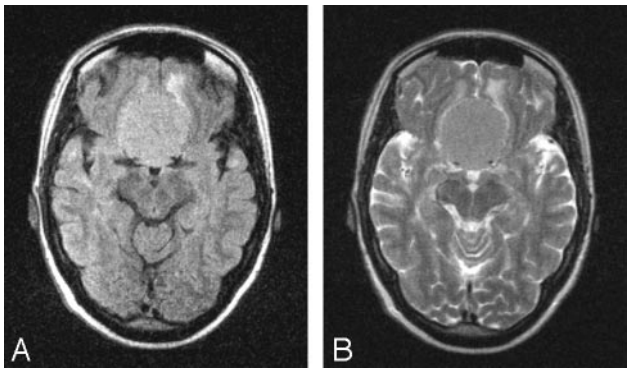

Fig 8. Meningothelial meningioma (*A*) FLAIR image (relative intensity of tumor, 1.11). *B*, T2-weighted image (relative intensity, 1.05). Surgical bleeding, grade 8 on VAS and blood loss during surgery, 700 mL; hardness 4 on VAS; collagen content, 1; progesterone receptor expression, 3; microvessel density, 151 microvessels/mm^2. Time to maximum enhancement in dynamic imaging was 22 seconds from the time point when contrast agent arrived in the veins.

low progesterone receptor expression and high collagen content. However, in the case of the more common hyperintense meningioma, surgical bleeding and blood loss cannot be predicted in individual patients. There is too large an amount of

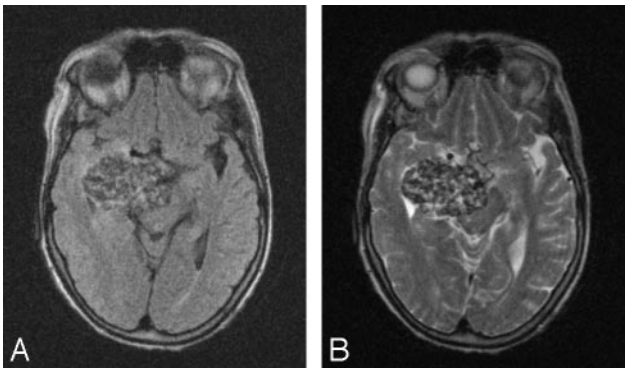

Fig 9. Fibrous meningioma (*A*) FLAIR image (relative intensity of tumor, 0.72). *B*, T2-weighted image (relative intensity, 0.83). Surgical bleeding, grade 1.5 on VAS and blood loss, 250 mL; hardness 7.5 on VAS; collagen content, 3; progesterone receptor expression, 0; microvessel density, 81 microvessels/mm^2. Time to maximum enhancement in dynamic imaging was 90 seconds from the time point when contrast agent arrived in the veins.

variation in these characteristics for any given level of hyperintensity.

Time to maximum enhancement was found to correlate strongly with microvessel density of meningioma. Shorter time to maximum enhancement predicts denser vasculature. This correlation should be clinically useful, especially in cases of deep-seated meningiomas that cannot be operated en bloc. Surgical bleeding of tumors having dense microvascularization may impede the operation because blood continually tends to cover the surgical cavity. The correlation is logical because the up-slope of the dynamic curve depends on tissue perfusion. CD34 staining does not indicate the functional state of the vasculature: all visible microvessels are not perfused at any given time. However, our results may actually be interpreted to show the relevance of microvessel attenuation as a measure of tumor perfusion because of its correlation with the time to maximum intensity.

The results support previous findings correlating hyperintensity in T2-weighted images with tissue softness.[5-7] Our results showing correlation between T2 intensity and vascularity are partly at odds with some earlier studies. In this study, the intensity in T2-weighted and FLAIR images correlated with the vascularity (surgical bleeding) as evaluated by the neuro-

surgeon as it did in the study of Chen et al.[5] However, these intensities did not correlate with the microvascular density as they did in the study of Maiuri et al.[22] The correlation of T2-weighted and FLAIR imaging with collagen content is in agreement with a previous study in which intensity on T2-weighted images was found to correlate with the percentage of collagen content in pituitary adenomas.[23] Lower signal intensities also in those tumors predicted more collagen. Results of the dynamic study agree with those of Nägele et al,[13] who found that highly vascularized meningiomas enhanced more rapidly than those with lesser vascularization. Maximum enhancement correlated in this study with microvessel density as in the study of Oka et al, [14] though the correlation was not as high as that between time to maximum enhancement and microvessel density. Association of microvessel density with proliferation marker was not found in the studied meningiomas, though in gliomas, this correlation has been found.[24] This difference may be due to the overall low proliferation rate typical for meningiomas. The dynamic curve shapes in this study were well in accordance with those reported by Ikushima et al.[11] In both studies, most of meningothelial meningiomas enhanced rapidly and then declined in intensity, whereas none of fibrous meningiomas showed this pattern.

Progesterone receptor expression seems to correlate with most of the imaging parameters used in this study. This finding may be useful because the absence of progesterone receptors has been related to the tendency of meningioma to recur and also to poor outcome.[25,26] It is unlikely that the receptors per se affect MR images, but the association may come across other tissue characteristics to which the receptors are related. One possible explanation may be the association of progesterone receptor expression with collagen content of meningioma ($\tau = -0.46$, $P = .003$).

The surgeons' evaluations of vascularity and consistency of tumor tissue were degraded by the fact that they were made by several surgeons. Because of the nature of the dynamic enhancement study, we were forced to exclude patients who had had preoperative tumor embolization. This choice may have caused selection bias against larger or more vascular tumors, though there were only a couple of these patients during the study period. The measurement of enhancement dynamics is bound to yield a higher proportion of inaccuracy in cases with rapid enhancement because of long sampling intervals (ie, imaging time per frame of dynamic images).

Our reasons to perform this study on a 0.23T scanner were manifold. The open 0.23T scanner is optimal for imaging claustrophobic, obese, or pediatric patients.[21] Imaging studies available to them should be similar to those available to patients imaged on high-field scanners. Furthermore, intraoperative MR imaging is advantageous during surgery of some deep-seated meningiomas. At our institution, the routine perioperative MR imaging protocol includes a preoperative imaging session in the intraoperative 0.23T scanner for navigation of an optimal location for craniotomy and surgical approach. Dynamic imaging of contrast enhancement can be conveniently performed in the same session. Indeed, 5 patients in this series later underwent surgery in the intraoperative MR imaging suite.

Conclusion

This was the first study predicting characteristics of meningiomas with low-field MR imaging, including dynamic contrast-enhancement assessment. We attained results similar to those attained on high-field scanners. A positive correlation was found between progesterone receptor expression and relative intensity of tumor on FLAIR images. A negative correlation was found between the previously mentioned intensity and grade of collagen content in meningioma tissue. Surgical bleeding and blood loss correlated moderately with relative intensity on FLAIR images. Time to maximum enhancement derived from dynamic T1-weighted imaging predicts microvascular density of meningioma tissue. According to this and previous studies, MR imaging cannot give definitive answers to questions of consistency, vascularity, and histologic parameters of meningiomas in all patients. However, in some cases, it may still give predictions that should be taken into account when planning surgery of meningioma in a critical location. Further studies with larger numbers of patients are still needed to establish the full potential of this imaging scheme.

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