Original Investigation

Correlation of Preoperative Radiological Evaluation of Skull and Non-skull Base Meningiomas with Clinical and Surgical Data

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ABSTRACT

AIM: To determine whether neuroradiological assessment of skull and nonskull base meningioma consistency and vascularity can be used to improve the surgical approach.

MATERIAL and METHODS: Forty meningioma cases were split into skull (n = 16) and nonskull (n = 24) base groups, and intraoperative surgical reports of observed tumor consistency (stiffness) and vascularity were compared with preoperative neuroradiological magnetic resonance (MR) perfusion and postoperative histopathological analysis of collagen and CD34 levels.

RESULTS: The skull base group had significantly higher CD34 levels (P = 0.004) than the nonskull base group. Further comparison of CD34 levels also revealed significantly higher CD34 levels (P = 0.032) in transitional versus fibroblastic subtypes. Observation-based vascularity scoring did not reveal a significant correlation between tumor grade and relative cerebral blood volume (P = 0.604). In contrast, there was a statistically modest, but significant, correlation between intraoperative observation-based consistency and Verhoeff-van Gieson collagen scores (rs = 0.400).

CONCLUSION: Preoperative assessment of consistency and vascularity using MR imaging was ambiguous. Overall, one of the most important limiting factors was the subjective observational assessment of tumor consistency and vascularity by surgical teams.

KEYWORDS: Meningioma, Magnetic resonance perfusion, Magnetic resonance imaging, Tumor stiffness, Tumor vascularity

ABBREVIATIONS: CBV: Cerebral blood volume, **rCBV:** Relative cerebral blood volume, **FLAIR:** Fluid-attenuated inversion recovery, **MR:** Magnetic resonance, **MRI:** Magnetic resonance imaging, **ROI:** Region of interest, **VVG:** Verhoeff-van Gieson

■ INTRODUCTION

Meningiomas are mostly benign tumors (90%) that arise from arachnoid cap cells commonly between the fourth and sixth decades of life. They predominantly occur in women and constitute 13%–26% of primary brain tumors and one in every four spinal cord tumors (9). Preoperative surgical evaluation of tumor consistency and vascularity is important, especially for those that are deep-seated and/or located at the skull base, because these characteristics influence the surgical approach and success rates. Therefore, the present study evaluated whether preoperative cranial magnetic resonance (MR) imaging (MRI)

of the consistency and vascularity of skull and nonskull base meningiomas can be used to improve current surgical approaches, techniques, and planning.

■ MATERIAL and METHODS

The current study evaluated the surgical reports of 40 subjects with meningioma who underwent surgical resection via standard methods. All surgeries were conducted by the same surgeon, and surgical observations were assessed with a subjective scoring system which rated each tumor's intraoperative consistency and vascularity on a scale from 1 to 10. For consistency, a score of 1 denoted extremely soft tumors, while 10 denoted extremely firm; tumor consistency (stiffness) was determined by surgical observation while using a Cavitron Ultrasonic Surgical Aspirator. For vascularity, a score of 1 denoted a nonhemorrhagic tumor, whereas 10 denoted a tumor with uncontrolled hemorrhage; intraoperative bleeding was quantified by measuring the amount of blood collected during resection. Resected tissues were fixed with 10% buffered formalin and embedded in paraffin blocks, and prepared sections were stained with hematoxylin and eosin. Select blocks of hematoxylin and eosin-stained sections from each case were further assessed by immunohistochemistry and Verhoeff-van Gieson (VVG) staining.

Immunohistochemical analysis of CD34 was performed with an automated staining device (BenchMark XT IHK/ISH Staining Module, Ventana Medical Systems Inc., Medical Systems, Tucson, AZ, USA). Fixed tumor sections (4-μm thickness) were incubated on positively-charged glass slides overnight at 40°C. After deparaffinization by passing through compatible solutions, slides were immersed in gradually decreasing concentrations of alcohol before rehydrating with distilled water. Antigen retrieval was performed by incubating with buffered citrate solution for 30 min at 36°C, before incubating with a commercially available CD34 (clone QBEnd/10) antibody (1:400; Thermo Scientific Lab Vision Corp., Fremont, CA, USA) and incubating for 20 min. After, reverse staining was performed with 0.01% hematoxylin and then slides were washed. Since every slide showed positive staining, additional control tissue was not necessary.

To assess microvascular density, slides were screened at 40× and 100× magnification before counting positively-stained cells and/or cell clusters in three areas per slide with the highest vascular density at 400× magnification. Positively-stained cells/cell clusters were considered part of the microvascular structure regardless of whether a lumen was present. The presence of red blood cells was not accepted as a criterion for vessel count. The mean CD34-positive cell/cell cluster count of all three areas on each slide was considered to be directly proportional to the mean microvascular density.

Fixed tissue sections were divided into four groups for VVG analysis of collagen content: Group 1, 0%–5% staining; Group 2, 5%–25% staining; Group 3, 25%–50% staining; Group 4, ≥50% staining. Sections were then assessed using an Olympus BX50 microscope.

MRI was performed with a 1.5-T magnet (Symphony; Siemens Medical Systems, Erlangen, Germany) using coils for 16-channel cerebral imaging. Prior to administration of contrast material, sagittal and axial T1A spin echo (repetition/echo time: 508/17 ms, matrix: 320 × 189, slice thickness: 5 mm, gap: 2 mm, field of view: 23 cm) and axial fluid-attenuated inversion recovery [FLAIR] (repetition/echo time: 8020/119 ms, inversion time: 2390 ms, matrix: 320 × 188) sequences were obtained. After, 15 mL of contrast material (Gd-diethylenetriamine penta-acetic acid, 0.2 mmol/kg) was intravenously administered at 5 mL/s by an automatized pump (Medrad® Spectris Solaris® EP), followed by administration of bolus serum physiologic solution (20 mL). Five minutes after contrast injection, T2A dynamic susceptibility perfusion series images were acquired at a gradient-echo echo-planar sequence (repetition/echo time: 1560/30 ms, flip angle: 90, bandwidth: 1502 Hz/Px, matrix 128 × 128, slice thickness: 5 mm, gap: 2 mm, field of view: 23 cm, acquisition time: central subligamentous disc protrusion min. 24 s). A total of 21 post-contrast T1A sagittal, axial, and coronal sequences parallel to each other were acquired.

Dynamic images were processed with perfusion application software. Cerebral blood volume (CBV) maps were assessed according to pixels such that the region of interest (ROI) had a mean of 30 pixels (ROIs with <20 pixels were excluded). Assessment of ROIs was repeated three times from the solid part of the tumor where it was most color-coded to determine the mean relative CBV (rCBV). The rCBV was calculated by dividing the tumor CBV by the CBV of the white matter in the normal contralateral cerebral hemisphere.

Skull base meningiomas were defined as localization 1, and convexity, falx, and parasagittal (nonskull base) meningiomas were defined as localization 2. The amount of edema in the meningiomas were rated from 0 (nonedematous) to 3 (extensive edema). Meningiomas were also pathologically stratified as transitional, fibroblastic, atypical, angiomatous, or other types.

Statistical analyses were performed with Number Cruncher Statistical System 2007 and Power Analysis and Sample Size 2008 Software (UT, USA). Data were analyzed descriptively by mean standard deviation, median, frequency, percentage, minimum, and maximum. For non-normally distributed quantitative data, Mann–Whitney U-test and Kruskal–Wallis test were used to make comparisons between two or more groups, respectively. Assessment of association between parameters was performed through Spearman's correlation analysis. Statistical significance was set at $p < 0.01$ and $p < 0.05$.

■ RESULTS

Data were gathered from eight male (20%) and 32 female (80%) patients. The mean age was 53.9 ± 11.7 years (range: 29–79 years). World Health Organization Grade I tumors were detected in 32 subjects (80%), while the remaining eight subjects (20%) were classified as Grade II. Pathologically, there were 18 patients (45%) with transitional type meningioma, 10 (25%) with fibroblastic, 8 (20%) with atypical, 2 (5%) with angiomatous, 1 (2.5%) with meningotheliomatous, and 1 (2.5%) with secretory type meningioma. Sixteen subjects (37.5%) had skull base tumors, while the other 24 (62.5%) had

convexity, parasagittal region, and falx (nonskull base) tumors. The majority of tumors (70%; n = 28) were smaller than 5 cm in diameter, and the remaining 30% (n = 12) were larger in size. Neuroradiological assessment revealed nine subjects (22.5%) had nonedematous tumors (score = 0), 7 (17.5%) had extensive edema (score = 3), and 24 had intermediate edema (score of 1: 37.5%, n = 15; score of 2: 22.5%, n = 9; Table I). According to the observation-based scoring, perioperative vascularity scores ranged from 2 to 8 (mean: 3.57 ± 1.58), and perioperative consistency (stiffness) scores ranged from 1 to 9 (mean: 4.92 ± 2.06).

The number of CD34-positive cells/cell clusters varied between 61 and 402 (mean: 157.22 ± 77.15), and numbers significantly differed by the pathological type of tumor (p = 0.032; p < 0.05). Pairwise comparisons showed significantly more CD34 positivity in those with transitional compared to fibroblastic type meningiomas (p = 0.010; p < 0.05). No statistically significant difference was observed between any of the other pathological types (p > 0.05). CD34 positivity also differed by tumor localization, with significantly more CD34 positivity being observed in skull base than nonskull base tumors (p = 0.001; p < 0.01).

VVG collagen scores varied between 1 and 4, with a mean of 2.32 ± 0.85 (Figure 1); 17.5% (n = 7) had a score of 1.40% (n = 16) had a score of 2.35% (n = 14) had a score of 3, and 7.5% (n = 3) had a score of 4. VVG collagen scores also differed significantly by the pathological type of tumor (p = 0.032; p < 0.05). Transitional type tumors had significantly higher VVG collagen scores than atypical types (p = 0.004; p < 0.01). No significant differences were detected among other pathological types (p > 0.05, Figure 3).

Mean tumor and normal white matter CBV values were 277.67 ± 1157.42 (range: 289.2–4095) and 306.75 ± 141.61 (range: 44.3–630.2), respectively, resulting in a mean rCBV of 9.66 ± 3.93 (range: 3.96–18). CBV values differed significantly by the pathological type of tumor (p = 0.022; p < 0.05). Although pairwise comparisons indicated that transitional type meningiomas had obviously elevated CBV values compared with the fibroblastic type, this difference was not statistically significant (p = 0.055; p > 0.05). However, the CBV values of fibroblastic type tumors were significantly lower than that of the atypical type (p = 0.013; p < 0.05). No significant differences were detected among any of the other groups (p > 0.05, Figure 2).

No significant association was found between perioperative consistency scores and CD34 positivity, CBV values, or rCBV values (p > 0.05). Although a slight positive association was found between perioperative consistency and VVG collagen scores, it was not statistically significant (r = 0.275; p = 0.086; p > 0.05). Likewise, perioperative vascularity scores were not significantly correlated with CD34 or rCBV values (p > 0.05). While perioperative vascularity scores and CBV values showed a somewhat positive association, it was not statistically significant (r = 0.074; p = 0.087; p > 0.05). Unlike consistency, perioperative vascularity and VVG collagen scores showed a slightly negative, but not statistically significant, correlation (r = -0.283; p = 0.077; p > 0.05). Furthermore, perioperative consistency scores, vascularity scores, and rCBV values did not show statistically significant differences when compared by pathological tumor type (p > 0.05).

■ DISCUSSION

Surgical resection of Grade I meningiomas often has a very good prognosis. Therefore, it is critical to manage these tumors as soon as possible to minimize morbidity. Important factors associated with successful treatment include tumor localization, size, relation to neural and vascular structures, consistency (stiffness), vascularity, and probable histopathological diagnosis in preoperative evaluation. Among these, consistency and vascularity are the most difficult to reliably determine by available conventional assessment
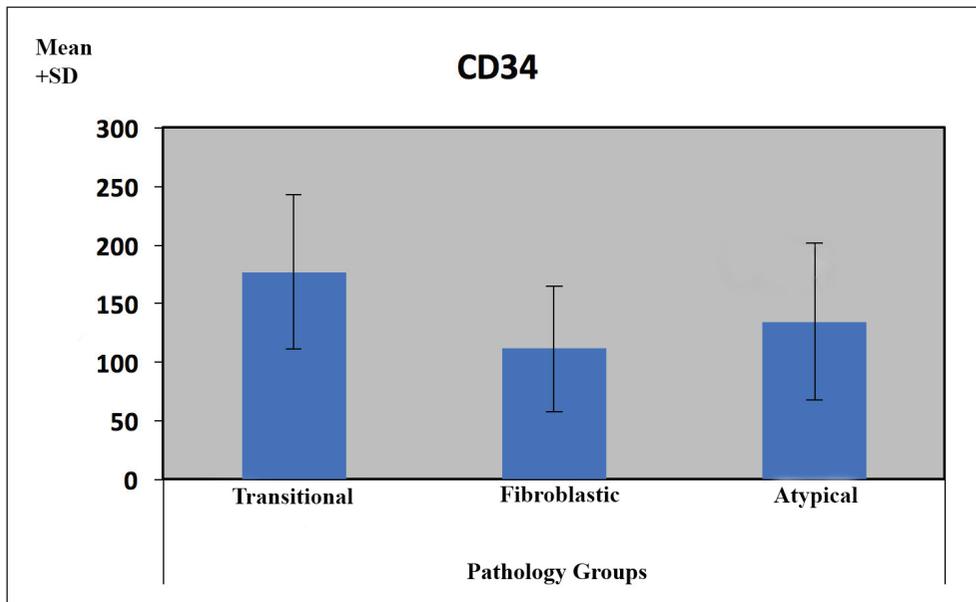

Figure 1: CD34 according to pathological groups.

Table I: Patients' Characteristics, Radiological and Histopathological Features

Case	Localization	Age	Gender	**Size	***Edema	Perioperative bleeding score	Perioperative consistency score	****Pathology Group	Grade	CD34	EVG-collagen score	CBV mass	CBV normal tissue	rCBV
1	1	47	F	2	2	3	6	2	1	132	3	3812.7	244.3	15.606631
2	2	55	F	1	1	5	1	3	2	61	1	4034.3	484.8	8.3215759
3	2	57	F	2	3	3	6	3	2	119	2	4081.8	325.8	12.528545
4	2	42	M	1	1	6	1	3	2	206	3	3971.6	236.4	16.800338
5	1	63	F	2	3	2	6	5	1	100	3	4095	319.1	12.832968
6	2	47	M	1	1	3	4	1	1	87	2	2064.7	293.5	7.034753
7	2	42	M	1	1	8	7	1	1	151	2	3481.1	198	17.581313
8	1	39	F	2	0	2	7	1	1	351	4	3230.8	288.3	11.206382
9	1	54	F	2	1	4	5	1	1	212	3	3770.5	209.4	18.006208
10	1	66	F	2	1	3	6	1	1	205	3	3967.8	489.3	8.1091355
11	2	67	F	1	3	4	3	1	1	108	3	3265	197.1	16.565195
12	1	55	M	1	2	8	2	3	2	235	1	4095	304.5	13.448276
13	2	44	F	2	1	2	3	2	1	63	2	1934	246.8	7.8363047
14	2	54	F	2	2	3	3	2	1	79	4	678.2	171.1	3.9637639
15	2	69	M	1	2	3	3	3	2	75	2	3598.7	285	12.627018
16	1	34	F	2	0	3	4	5	1	176	3	1681.3	241.9	6.9503927
17	1	56	M	1	2	4	2	4	1	230	2	3000	434.9	6.8981375
18	2	44	F	2	3	4	3	3	2	79	2	2528.8	630.2	4.0126944
19	2	52	F	2	1	3	6	3	2	190	1	961.2	183.4	5.2410033
20	1	50	F	2	0	3	7	1	1	135	4	670.2	90.7	7.3891951
21	1	54	F	1	2	4	4	1	1	170	2	3986.5	366.1	10.889101
22	2	34	F	2	1	3	3	2	1	227	2	1609.1	183.6	8.7641612
23	2	53	M	2	2	3	6	2	1	121	2	2052.8	371.1	5.5316626
24	1	40	F	2	0	2	6	1	1	212	2	3186.4	450.7	7.0698913
25	2	79	F	1	2	6	7	1	1	219	2	3971.7	450.7	8.812292
26	2	70	F	2	3	2	7	1	1	217	3	289.2	44.3	6.5282167
27	2	69	F	2	0	2	7	2	1	152	3	3259.1	299.3	10.889075
28	1	62	F	2	1	3	3	1	1	152	2	1860.4	219.8	8.4640582
29	1	52	F	1	3	4	5	1	1	152	2	4060.6	472.7	8.5902264
30	2	38	F	1	1	5	8	2	1	62	3	2386.5	284.1	8.4002112
31	1	64	F	2	0	2	8	1	1	262	3	3226	430.2	7.4988377
32	2	64	F	2	0	3	4	2	1	140	2	2295.2	217.8	10.538108
33	2	66	F	2	1	3	4	1	1	154	3	3115.4	630.2	4.94351
34	2	65	F	2	3	2	9	1	1	99	3	2436	222.1	10.968032
35	2	29	F	2	1	2	7	3	2	112	1	3531.4	519.6	6.7963818
36	1	45	F	2	2	2	7	4	1	402	1	3110.4	220.8	14.086956
37	2	68	M	2	1	6	2	1	1	97	2	4000.7	473.8	8.4438581
38	2	61	F	2	1	6	4	2	1	79	1	1730.8	110.5	15.663348
39	2	57	F	2	0	4	5	2	1	61	1	647.8	103.9	6.2348411
40	2	49	F	2	0	3	6	1	1	205	3	1428.2	324.2	4.4053053

*1 (Group 1): Skull base; *2 (Group 2): Convexity, falx, and parasagittal
**Size 1: >5cm, **Size 2: <5cm
***Edema: 0-3, 0: No edema, 3: Severe edema
****Pathology Group 1: Transitionaltype, **Pathology Group 2:** Fibroblastic type, **Pathology Group 3:** Atypical.
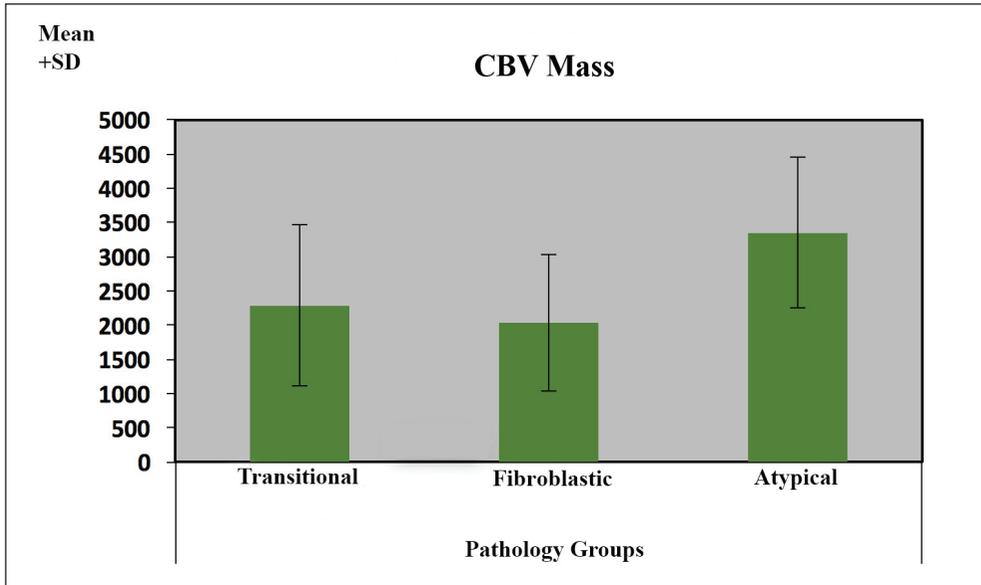
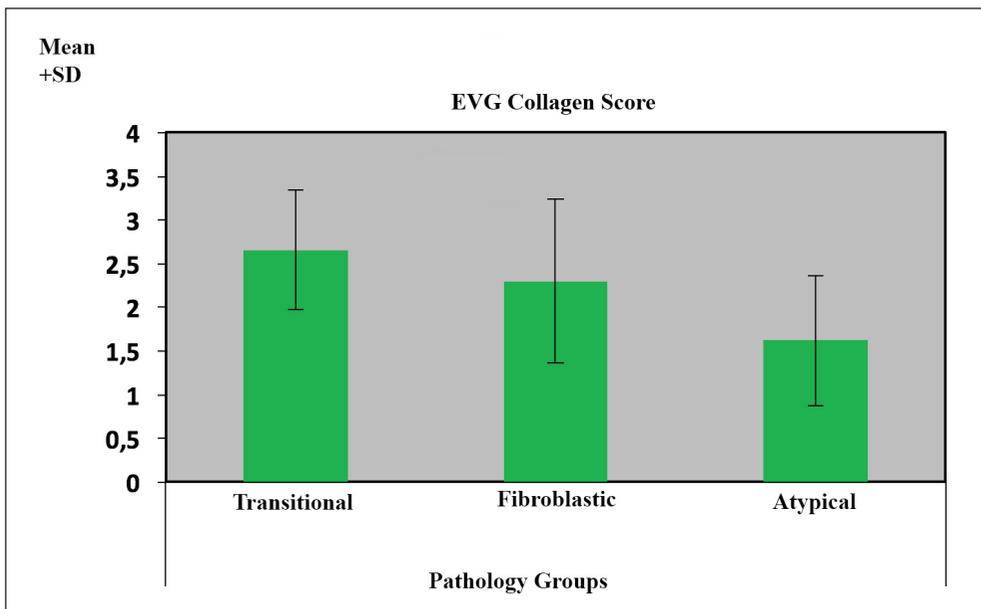**Figure 2:** CBV mass CVB according to pathological groups.

Figure 3: EVG collagen score.

methods. In the present study, meningiomas were evaluated by dividing them based on skull and nonskull base localization. This stratification is based on a report suggesting that tumors within these different locations have embryologically originated from different dura. In their observational study, Sade et al. reported that Grade II and III meningiomas rarely arose from the skull base but were relatively common elsewhere (7), while skull base meningiomas were usually Grade I. However, sufficient practical knowledge about the vascularization, consistency, and histopathological features of each type is lacking.

Herein, 10 out of 14 (71%) skull base tumors were pathologically transitional with the rest being fibroblastic, whereas only seven (35%) out of 20 nonskull base tumors were classified as transitional; of the remaining meningiomas, seven were fibroblastic and six were atypical. In addition, CD34 levels (i.e., microvascular density) were significantly elevated in skull versus nonskull base tumors (P = 0.004), and mean CBV and rCBV values indicated slightly greater blood flow and perfusion in skull base tumors than in nonskull base tumors, though not significant. Comparison of microvascular density between pathological types of meningioma also revealed significantly higher CD34 positivity in transitional tumors than in fibroblastic types. Since the majority of skull base tumors were pathologically transitional, these results suggested that skull base meningiomas tend to have higher microvascular density and are more vascular than nonskull base tumors. However, these two pathological types did not significantly differ in terms of perioperative vascularity score,

and perioperative vascularity did not significantly correlate with CD34 positivity or rCBV values. These results are in agreement with those reported by Yrjänä et al. showing no significant correlations between CD34-positivity and vascularity when comparing T1A, T2A, and FLAIR MRI sequences with histopathological data (14). Nonetheless, the current results indicated the possibility of increased vascularity in skull base tumors; therefore, more careful preoperative assessments are recommended.

It should also be noted that intense contrast enhancement of the tumor is not necessarily associated with its vascularity. While MR perfusion may be recommended for obtaining information about vascularity, further research with a larger sample size is warranted. Several MR perfusion studies have reported a significant association between Grade I, II, and III tumors and rCBV values (4,5,12,18), while other studies have advocated the opposite (12,17,18). In the present study, a significant association between tumor Grade and rCBV value was not found. However, the CBV value of atypical meningiomas was higher than that of transitional and fibroblastic types, implying a possible association between higher rates of recurrence and elevated blood flow at the tumor site. This is further supported by the higher CD34 levels in transitional compared to fibroblastic tumors.

In addition to objective measure, the importance of intraoperative real-time surgical inspection of the tissue accompanied by the surgeon's opinion should be emphasized. Despite its subjectivity, the surgeon's report on the bleeding rate does play a guiding role in the surgical process. Nevertheless, intraoperative bleeding rate (vascularity) was not significantly associated with CD34 or rCBV values in the current study. This could be attributable to the subjectivity of the assessment, which is based on the experience of surgical team and limited number of cases. It may also originate from the difference in tumor localization and surgical access route. In addition, detection of higher CD34 levels may partially reduce this possibility. However, the positive but non-significant association between vascularity score and CBV values revealed in the present study suggests significance by increasing the number of analyzed cases. Furthermore, the negative correlation between vascularity and VVG collagen scores indicated lower bleeding rates in consistent (firm) tumors.

Maximum surgical resection is very important for survival in meningioma cases (2), and preoperative prediction of meningioma consistency helps determine the best surgical corridor, especially for deep-seated skull base tumors. For instance, while a petroclival and comparably softer meningioma can be resected by a retrosigmoid approach without additional morbidity or cranial nerve injury, using the same approach on a consistent (firm) meningioma in the same location would be very challenging. In cases of firm petroclival meningiomas, a presigmoid approach is preferable. In addition, the size of the lesion has an impact on selection of the surgical technique. In the present study, surgical teams numerically rated the consistency of each meningioma (subjective). Unlike subjective vascularity data, comparison of subjective consistency with objective VVG collagen scores revealed a positive but non-significant correlation. Importantly,

this indicates that subjective surgical opinions are a beneficial and usable parameter for correlation analysis between tumor consistency and radiological data. Furthermore, this suggests that while the surgeon's assessment of intraoperative vascularity is more subjective, consistency is a more common and statistically reliable opinion (i.e., a meningioma would be classified as consistent by both a surgeon familiar with meningioma surgery and one that is not).

Comparison of transitional meningiomas with fibroblastic types, which are known to be more consistent, did not reveal a statistically significant difference between VVG collagen and intraoperative consistency scores (P = 0.985). However, this was attributed to the limited number of fibroblastic cases included in the present study, and future studies with a larger sample size might produce significant results. However, VVG collagen scores of transitional meningiomas were significantly higher than those of the atypical type (P = 0.004; P < 0.01). The statistically significant increase in VVG collagen scores of transitional meningiomas, which outnumbered atypical types, may favor its use as an objective criterion for determining tumor consistency. This also supports the notion that even a small number of fibroblastic cases could moderate significant differences between transitional and fibroblastic tumors.

Although previous studies using computed tomography, classic MRI, MR spectroscopy, and/or MR diffusion have reported statistically significant findings between soft and consistent (firm) tumors, the reliability of these techniques is hampered by low sensitivity and specificity (3,4,8,11). Newer techniques, such as MR elastography, have also been shown to be effective for direct measure of mechanical characteristics of brain tumors (10). Murphy et al. examined meningioma consistency by preoperative 3-T MR elastography and reported favorable outcomes in moderately consistent meningiomas (6). Use of routine MR perfusion in the present study, however, did not reveal a significant correlation between subjective surgical observations and objective histopathological findings. We thought that it was important to normalize tumor consistency according to surrounding brain tissue. Sımilar to a study by Alyamany et al. (1), ROIs measurements were made in FLAIR, T2, and diffusion MRI sequences in the current study and intraoperative observations were graded based on Cavitron Ultrasonic Surgical Aspirator absorption levels. However, while they found significant correlations between T2 and FLAIR sequences and Cavitron Ultrasonic Surgical Aspirator absorption levels (1), the current results did not find a significant correlation between rCBV values and intraoperative consistency scores. Yao et al. provides insight into this discrepancy by stating that although MRI is not a marker for pathological analysis, T2 signals may provide some clues (13).

■ CONCLUSIONS

Overall, the current results suggest that preoperative MR perfusion imaging may not provide definitive data regarding the consistency and vascularity of either skull or nonskull base meningiomas. However, it is thought that much more useful information could be gained by increasing the sample size and evaluating additional MRI sequences. Although the subjective

assessment of vascularity and consistency by surgical teams during resection is an central limitation to the current results, it was minimized by only examining cases attended by the same surgeon. Furthermore, subjective perioperative results were compared and correlated with postoperative objective pathological analyses to statistically verify the reliability of certain aspects of surgical reports. This is in accord with Zada et al. who suggested using a standard model and correlating it with postoperative pathological analysis to minimize subjectivity during intraoperative observations (1,13,15).

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