Type of article: Original Article

Title: Predicting the Consistency of Meningiomas Preoperatively Using Magnetic Resonance Imaging

Running Title: Meningioma Consistency on MRI

Authors: Seema Rohilla [1]*, Orcid ID: 0000-0002-1424-5792

Shweta Yadav[1], Orcid ID: 0000-0003-0707-2712
Department of Radiodiagnosis, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India.

Ishwar Singh[2], Orcid ID: 0000-0003-3547-3097
E-mail: drishwarsingh@yahoo.co.in

1- Department of Radiodiagnosis, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India.

2- Department of Neurosurgery, Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India.

Corresponding Author:
Seema Rohilla,
Department of Radiodiagnosis, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India.
E-mail: seemarohilla@yahoo.co.in
Phone: 919815647659

Highlights

- The tumor/cerebellar peduncle T2W signal intensity ratio (TCTI ratio) could predict the consistency of meningioma and the results were statistically significant ($p<0.05$).
- A cut-off TCTI value of 1.5 demonstrated 78% sensitivity and 75% specificity in differentiating firm from soft meningiomas.
- The mean TCTI ratio was 1.44 for firm and 1.65 for soft meningiomas.
- There was no significant correlation between consistency and diffusion tensor imaging (DTI) parameters or magnetization transfer ratio (MTR).

Plain Language Summary

The present study was undertaken to assess the consistency of meningiomas preoperatively using MRI to assist surgeons in deciding on the surgical approach and predicting the need for staged resection or expected subtotal resection. Firm tumors are comparatively difficult to remove and may not be completely resected. Soft tumors are removed more easily and may even be aspirated. Only one MRI parameter, namely TCTI ratio (the ratio of signal intensity of the tumor to that of the cerebellar peduncle on T2W images), significantly correlated with meningioma consistency and successfully aided in this distinction. The TCTI ratio was higher in soft meningiomas compared to firm meningiomas. With a cut-off value of 1.5 for the TCTI ratio, firm and soft meningiomas could be distinguished in 78 out of 100 cases. In 75 out of 100 cases, the tumor consistency matched the prediction made by this ratio. This distinction can also help patients better understand the surgical outcome.

Abstract

Background and Aim: Knowledge of the consistency of meningioma is very helpful for neurosurgeons during surgery. Our study aimed to objectively demonstrate the effectiveness of the tumor/cerebellar peduncle T2-weighted imaging intensity (TCTI) ratio, diffusion tensor imaging (DTI), and magnetization transfer ratio (MTR) in predicting the consistency of meningiomas.

Methods and Materials/Patients: Twenty-five patients with meningiomas were examined using three Tesla MR (Discovery 750w with GEM Suite from GE, Milwaukee, WI, USA) imaging. T1W, T2W, T2W/FLAIR, DWI, DTI, and MT sequences were performed. Regions of interest (ROIs) were drawn on the tumor and cerebellar peduncle, and the TCTI ratio was calculated. Similarly, ROIs were drawn on Magnetization Transfer Images (MT on and MT off images), and the magnetization transfer ratio (MTR) was calculated. DTI data were transferred to ReadyView software, where ROIs were placed on the tumor, and fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were calculated. Tumor consistency was correlated with the TCTI ratio, FA, MD, AD, RD, and MTR.

Results: Out of 25 meningiomas, nine were soft and 16 were firm. The Wilcoxon-Mann-Whitney U test comparing these groups was statistically significant only for the TCTI ratio. The mean TCTI ratio in firm meningiomas was 1.44, while in soft meningiomas it was 1.65. A single cutoff TCTI value of 1.5 for soft versus firm tumors was found to be 78% sensitive and 75% specific. There was no significant correlation between consistency and DTI parameters or MTR.

Conclusion: The TCTI ratio showed a significant correlation with the consistency of meningiomas with fair sensitivity and specificity. However, MTR, fractional anisotropy, and mean, axial, and radial diffusivities failed to show a significant correlation with the consistency of meningioma.

Keywords: Meningioma consistency; TCTI ratio; Diffusion tensor Imaging; Magnetization Transfer Ratio (MTR); Fractional Anisotropy

1. Introduction:

Meningiomas account for 16 to 20% of all cerebral tumors and are the most prevalent non-glial tumors of the central nervous system (CNS) [1]. The extent of resection and the surgical method can be affected by tumor vascularization, consistency, and surgical plane. In meningiomas of the skull base and those near neurovascular systems, these variables are more important. Hard tumors that are adherent to neighboring vital structures, such as the internal carotid artery, optic chiasm, and cranial nerves, carry a higher risk of surgical morbidity and necessitate meticulous dissection procedures for removal [2]. Surgical resection is accomplished by first devascularizing the tumor from the surrounding area of the capsule and then debulking it from the center [3]. One of the key factors in removing the entire tumor while avoiding neurological deficits is the consistency of meningiomas [4]. The surgical approach chosen may be partially determined by the ability to accurately predict the consistency of a meningioma preoperatively based on neuroimaging studies. This ability may also provide additional information about the need for staged resection, expected subtotal resection, or other challenges related to consistency and/or vascularity [5].

Most of the studies conducted previously indicate the role of T2-weighted imaging in predicting the firmness of meningiomas preoperatively. The purpose of our study was to demonstrate the effectiveness of tumor/cerebellar peduncle T2-weighted imaging intensity (TCTI) ratio, diffusion tensor imaging (DTI), and magnetization transfer ratio (MTR) in predicting the consistency of tumors in the North Indian population in an objective manner.

2. Methods and Materials/Patients:

2.1 Subjects:

Twenty-five patients with meningiomas were studied, and those with previous cranial surgery/radiotherapy, as well as cases where the surgeon did not define the consistency of the tumor, were excluded. The study was approved by the Biomedical Research Ethics Committee of our institute before enrolling the first patient and was conducted following the principles outlined in the Helsinki Declaration of 1975, as revised in 2013. The study was approved under protocol number BREC/Th/20/Radiodiag09 on April 1st, 2021. Written informed consent was taken from the patients.

2.2 Imaging:

All patients were subjected to magnetic resonance imaging (MRI) on a 3T MRI system (GE, Discovery 750w with GEM Suite, Milwaukee, WI, USA) using a dedicated head coil with 32 channels.

The following sequences were performed: T1W (TE = 24 ms, TR = 2671.1 ms, FOV = 22 cm, slice thickness = 5.0 mm, slice spacing = 1.0 mm, frequency = 320, bandwidth = 41.67 kHz); T2W (TE = 114 ms, TR = 8901 ms, FOV = 22 cm, slice thickness = 5.0 mm, slice spacing = 1.0 mm, frequency = 512, bandwidth = 50 kHz); T2W/FLAIR (TE = 120 ms, TR = 10000 ms, FOV = 22 cm, slice thickness = 5.0 mm, slice spacing = 1.0 mm, frequency = 320, bandwidth = 31.25 kHz); DWI (TE = 83 ms, TR = 261 ms, FOV = 22 cm, slice thickness = 5.0 mm, slice spacing = 1.0 mm, frequency = 192, bandwidth = 166.7 kHz, b = 1000 s/mm²); DTI (TE = 78 ms, TR = 6413 ms, FOV = 22 cm, slice thickness = 4.0 mm, slice spacing = 1.0 mm, frequency = 128, bandwidth = 250 kHz, b = 1000 s/mm², diffusion directions = 30); and MT (TE = 15 ms, TR = 1300 ms, FOV = 24 cm, slice thickness = 5.0 mm, slice spacing = 1.0 mm, frequency = 256, bandwidth = 14.71 kHz).

ROIs were placed on both the tumor and the cerebellar peduncle on T2W images, and the ratio of signal intensities was calculated (TCTI ratio) (**Fig. 1**).

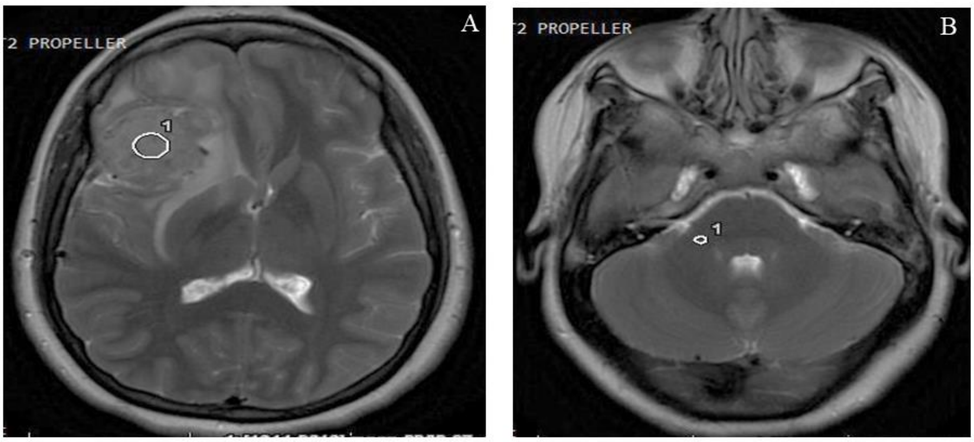

Fig.1: Calculating tumor to cerebellar T2 signal intensity (TCTI) ratio.

A) Region of interest (ROI) in tumor on T2 image and **B)** ROI in right middle cerebellar peduncle on T2 image.

TCTI ratio=signal intensity of ROI within tumor(A)/signal intensity of ROI within middle cerebellar peduncle (B)

The ROIs did not have any preset dimensions, as the size of meningioma was variable. In general, ROIs were made as large as possible to obtain the most representative sample of tumors on the axial sequence. In meningiomas with heterogeneous signal intensity, separate ROIs were placed within the tumor, and an average value was calculated. Likewise, ROIs were placed on the MT on and MT off images of the MT sequence, and the MT ratio was calculated (**Fig. 2**).

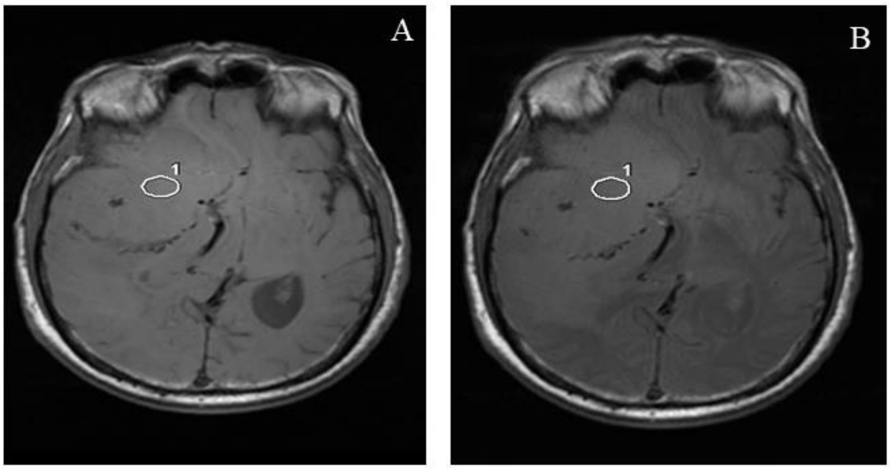

Fig.2: Calculating Magnetization transfer ratio.

A) M_o and **B)** M_s represent signal intensities without and with the magnetization transfer pulse.

MTR = $(M_o - M_s)/M_o$.

DTI data were transferred to ReadyView software, where the placement of the ROI on the tumor allowed for the calculation of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) by averaging the two minor eigenvalues (**Fig. 3**).

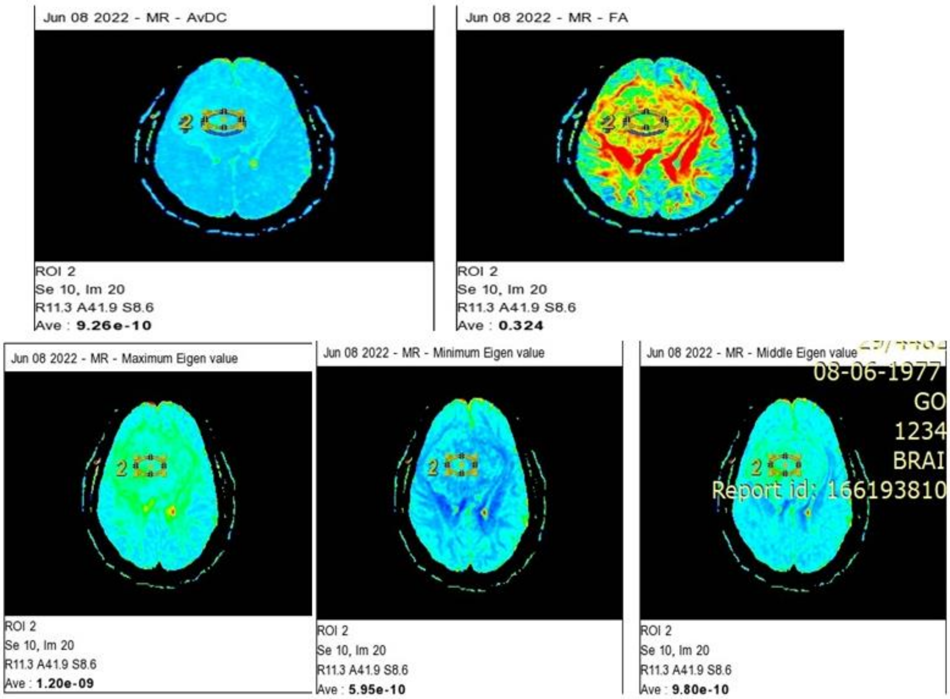

Fig.3: Calculating mean, axial and radial diffusivities. $\lambda_{\parallel} = \lambda_1 > \lambda_2 > \lambda_3$ and $\lambda_{\perp} = (\lambda_2 + \lambda_3)/2$, where $\lambda_{\parallel}$ =Axial diffusivity, $\lambda_{\perp}$ = Radial diffusivity, λ_1 =maximum eigen value, λ_2=middle eigen value and λ_3 =minimum eigen value.

Various parameters obtained were correlated with the intraoperative consistency of meningiomas.

2.3 Operative procedure:

During surgery, the consistency of the tumor was assessed and classified as soft for tumors that could be completely removed easily with a suction cannula, and hard for those requiring the use of surgical scissors, a scalpel blade, or a cavitron ultrasonic surgical aspirator (CUSA) set at a high amplitude, or for tumors that could not be removed by gentle manipulation. After exposure of the tumor, specimens were taken from different areas of the tumor and sent for histopathological examination to confirm the diagnosis.

2.4 Statistical analysis:

Data were analyzed using SPSS version 23. Means and standard deviations, as well as medians and interquartile ranges (IQRs), were calculated for continuous variables, while frequencies and percentages were calculated for categorical variables. Group comparisons for continuously distributed data were made using an independent samples t-test when comparing two groups. In cases of non-normally distributed data, appropriate non-parametric tests, specifically the Wilcoxon test, were used. The Chi-squared test was used for group comparisons of categorical data. Linear correlation between two continuous variables was explored using Pearson's correlation (for normally distributed data) and Spearman's correlation (for non-normally distributed data). Statistical significance was set at $p < 0.05$. For MRI findings showing a significant correlation with tumor consistency, receiver operator characteristic (ROC) analysis was performed to predict an optimal cut-off for a continuous predictor of a binary outcome. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated to assess the diagnostic performance of the predictors by creating a 2x2 cross-table with the outcome.

3. Results:

There were 11 males and 14 females, ranging in age from 18 to 68 years. There was no correlation between consistency and the size or location of the tumor, except for skull base tumors, where the majority (6 out of 7) of tumors were firm. There was no significant difference between soft and firm meningiomas in terms of T1, T2, and FLAIR signal intensity. However, all tumors that were hyperintense on T2W/FLAIR images were soft, while all tumors that were hypointense on T2W/FLAIR images were firm.

There was a significant difference in the TCTI ratio ($p=0.036$) between soft and firm tumors. Table 1 shows the consistency of meningioma with respect to the TCTI ratio. The area under the ROC curve (Fig. 4) for the TCTI ratio predicting soft versus firm consistency was 0.76 (95% CI 0.567 – 0.954), demonstrating fair diagnostic performance. At a cut-off of TCTI ratio ≥ 1.5, soft consistency of meningiomas was predicted with a sensitivity of 78%, and a specificity of 75%. Table 2 shows the diagnostic performance of the TCTI in predicting the consistency of meningiomas.

Table 1: Comparison of Soft Versus Firm Tumors in Terms of Tumor/Cerebellar Peduncle T2-Weighted Imaging Intensity (TCTI) Ratio (n = 25)

Tumor/Cerebellar Peduncle T2-Weighted Imaging Intensity (TCTI) Ratio	Surgical Assessment of Consistency		Wilcoxon-Mann-Whitney U Test	
	Firm	Soft	W	p-value
Mean (SD)	1.44 (0.30)	1.65 (0.20)	34.500	0.036
Median (IQR)	1.46 (1.26-1.54)	1.59 (1.5-1.72)		
Min – Max	1.01 - 2.14	1.41 - 1.96		

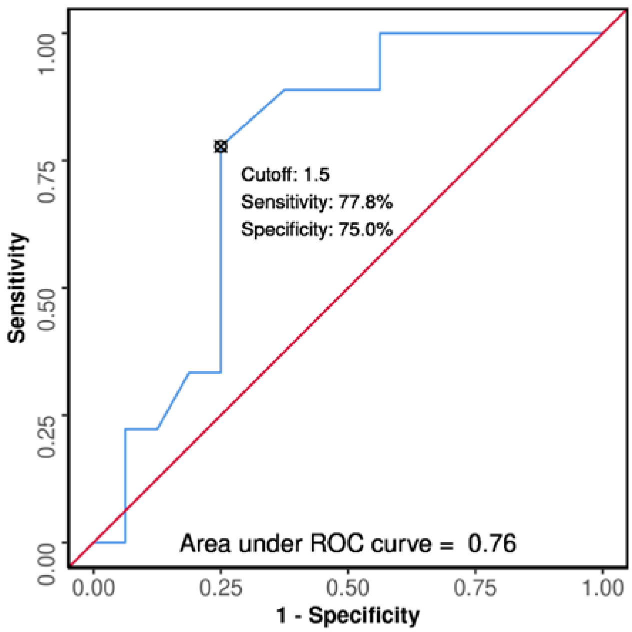

Fig.4: Receiver operating characteristic curve to determine the diagnostic accuracy of TCTI ratio.

Table 2: The Diagnostic Performance of Tumor/Cerebellar Peduncle T2-Weighted Imaging Intensity (TCTI) Ratio in Predicting the **Consistency of Meningiomas**

Parameter	Value (95% CI)
Cut-off (p-value)	≥ 1.5 (0.036)
Area Under the ROC Curve (AUC) (95% confidence interval)	0.76 (0.567 - 0.954)
Sensitivity	77.8% (40-97)
Specificity	75.0% (48-93)
Positive Predictive Value	63.6% (31-89)
Negative Predictive Value	85.7% (57-98)
Diagnostic Accuracy	76.0% (55-91)
Positive Likelihood Ratio	3.11 (1.24-7.79)
Negative Likelihood Ratio	0.3 (0.08-1.04)
Diagnostic Odds Ratio	10.5 (1.51-72.81)

There was no significant difference between the MT ratio of soft and firm meningiomas (p=0.375). Likewise, FA (p=0.169), MD (p=0.978), AD (p=0.590), and RD (p=0.522) did not correlate significantly with the consistency of meningiomas.

3.1 Correlation of histopathological types with the consistency of meningiomas

There were 11 meningothelial, five transitional, six fibroblastic, and three angiomatous meningiomas. There was a significant association between consistency and histopathological type (p=0.03) (Table 3).

Table 3: Association Between Surgical Assessment of Consistency and Histopathological Type (n = 25)

Histopathological Type	Surgical Assessment of Consistency			Fisher's Exact Test	
	Firm	Soft	Total	χ2	p-value
Meningothelial	7 (43.8%)	4 (44.4%)	11 (44.0%)		
Transitional	3 (18.8%)	2 (22.2%)	5 (20.0%)		
Angiomatous	0 (0.0%)	3 (33.3%)	3 (12.0%)	8.744	0.030
Fibroblastic	6 (37.5%)	0 (0.0%)	6 (24.0%)		
Total	16 (100.0%)	9 (100.0%)	25 (100.0%)		

All three angiomatous meningiomas were soft, while all six fibroblastic meningiomas were firm. However, meningothelial and transitional meningiomas did not show this strong correlation (Fig. 5).

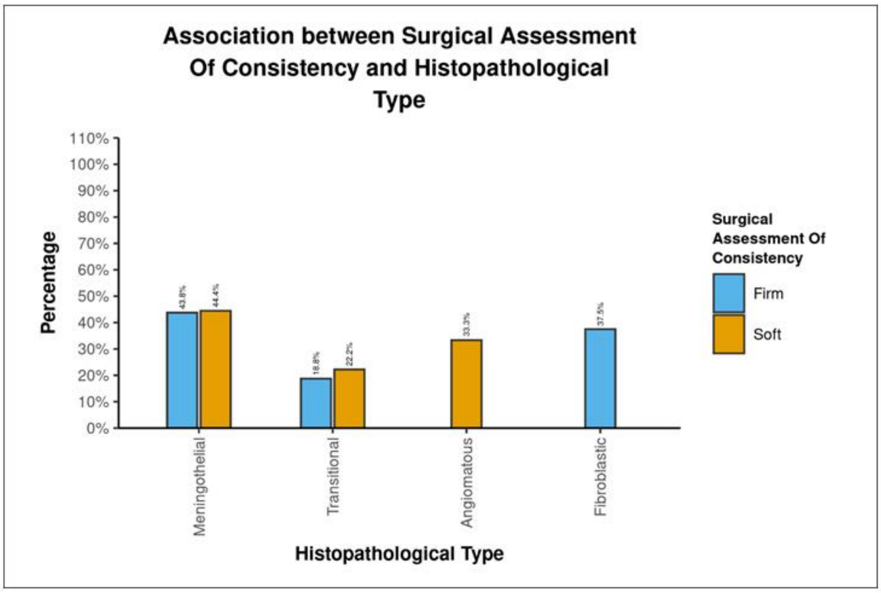

Fig.5: Bar graph showing association between histopathological types and percentage of firm/soft meningiomas.

Psammoma bodies were reported in five patients. Although there was no significant correlation between the presence of psammoma bodies and the consistency of meningiomas ($p = 0.123$), none of the meningiomas with psammoma bodies had soft consistency, and none of the soft tumors had psammoma bodies. This indicates that while not all firm tumors have psammoma bodies, the presence of psammoma bodies is an indicator of firmness (Fig. 6).

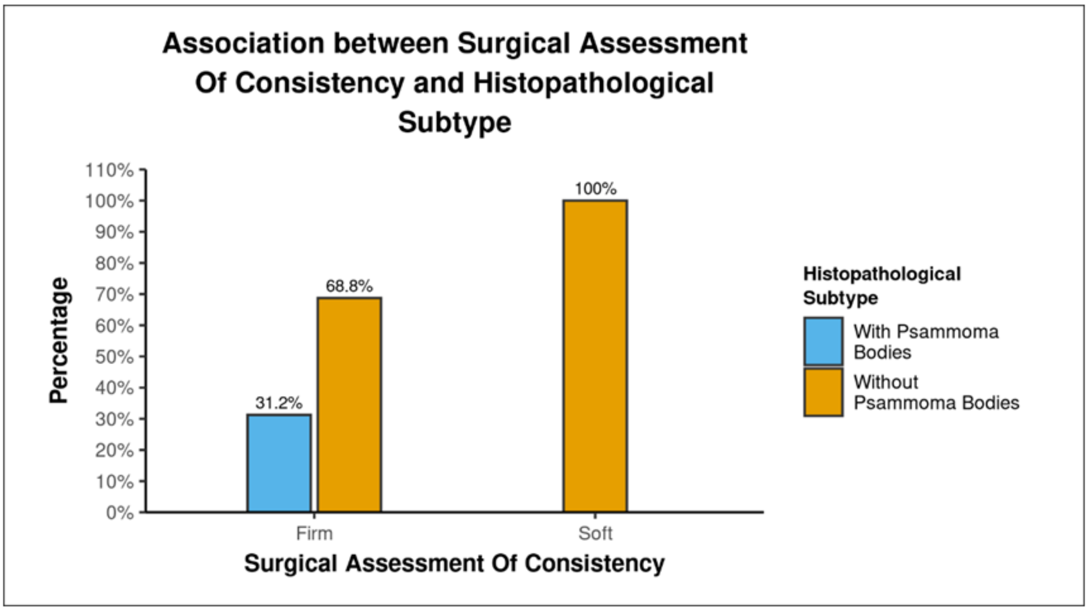

Fig.6: Bar graph showing association between consistency of tumor and presence of psammoma bodies on histopathology.

We found a significant difference between the presence and absence of psammoma bodies in terms of radial diffusivity (W = 17.000, p = 0.024), with the median radial diffusivity being highest in the meningiomas without psammoma bodies. The median radial diffusivity in the meningiomas without psammoma bodies was 0.78, while in meningiomas with psammoma bodies, it was 0.64. The median (IQR) FA in meningiomas with psammoma bodies was 0.33 (0.28-0.4), while in those without psammoma bodies, it was 0.18 (0.15-0.25) (p=0.024). This can easily be explained by the fact that psammomatous calcification obstructs free diffusion, giving directionality to diffusion and thus increasing FA while decreasing RD.

We were one of the few series to study the association between the histopathological type of meningioma and the MTR. There was a significant difference among the four histopathological types in terms of MTR ($\chi2$ = 8.656, p = 0.034), with the mean MTR being highest in the fibroblastic type. The mean for fibroblastic type was 0.26 (0.02), which was significantly higher than that of transitional meningiomas, with a mean of 0.19 (0.09).

3.2 Correlation of the CUSA score with the consistency of tumor

The CUSA was used in 13 patients. Ten meningiomas were suckable on CUSA with different amplitudes, while three were not suckable. The CUSA score correlated significantly (p = 0.037) with the consistency of meningioma (Table 4).

Table 4: Comparison of the Two Subgroups of the Variable Surgical Assessment of Consistency in Terms of CUSA Score **(n = 10)**

Cavitron ultrasonic surgical aspirator (CUSA) Score	Surgical Assessment of Consistency		Wilcoxon-Mann-Whitney U Test	
	Firm	Soft	W	p-value
Mean (SD)	87.50 (13.36)	37.50 (3.54)	16.000	0.037
Median (IQR)	87.5 (75-100)	37.5 (36.25-38.75)		
Min - Max	75 - 100	35 - 40		

The median (IQR) of the CUSA score in the firm group was 87.50 (75-100), while in soft meningiomas, it was 37.50 (36.25-38.75). The ROC curve for the CUSA score and the consistency of meningioma is shown in Figure 7. At a cutoff CUSA score of ≥75, it is possible to distinguish between firm and soft tumors with 100% sensitivity and 100% specificity.

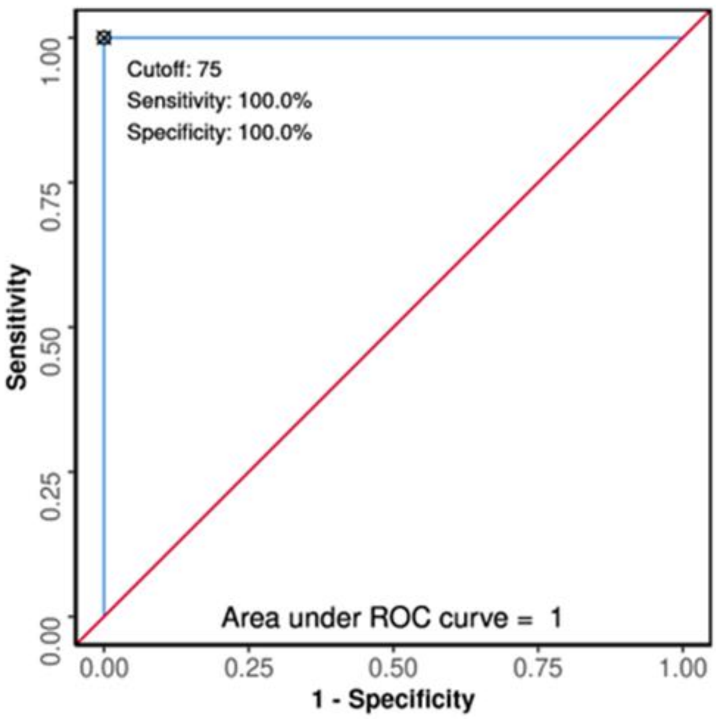

Fig.7: Receiver operating characteristic curve for CUSA score and consistency of meningioma.

4. Discussion

Preoperative planning is crucial for meningioma excision and is based on the position, size, and consistency of the tumor [6,7]. Consistency is a useful predictor of resectability, surgical complexity, and the time taken for surgery. Shorter operating times can be achieved by using suction or CUSA at a low setting to remove soft tumors. Harder tumors are more challenging to remove, increasing the level of surgical complexity and lengthening the duration of the procedure. The difficulty of resection increases if tumors encase neurovascular structures. Predicting meningioma consistency before surgery would enable more effective operative planning and selection of resection techniques [7]. This is crucial for the surgical outcome of tumors located in challenging sites, like the base of the skull [6], especially when meningiomas are increasingly being resected using minimally invasive techniques and the field of view is limited.

T2-weighted imaging has emerged as the most promising modality. Suzuki et al. also found a link between T2-weighted images and meningioma consistency, with hyperintense lesions being soft and hypointense lesions being hard [8]. Hoover et al. observed that, compared to gray matter, meningiomas that were T2 hypointense were almost always firm. Meningiomas with hyperintense T2WI signals and hypointense T1WI signals were more likely to be soft, whereas meningiomas with hypointense signals on T2WI and isointense signals on T1WI were more likely to be firm [9]. However, they reported having poor sensitivity in identifying hard tumors.

Fifty-six percent of meningiomas were reported to be nearly isointense with the cortical grey matter [10]. Our study corroborated with the literature, as 48% of our tumors were isointense to the cortex. Carpeggiani et al., Kashimura et al., and Romani et al., also found no relationship between MRI signal intensity and consistency [5,6,11]. We also did not find any significant correlation between the consistency of meningiomas with T1, T2, and FLAIR signal intensity, although the TCTI ratio was significant in this differentiation.

The intensity of reconstructed MR images is based on arbitrary units. Hence, direct comparisons between several acquisitions cannot be made. The pulse sequence or hardware design is vendor-specific. Being subjective, visual signal intensity measurement can be challenging, especially in large tumors with varied signal intensities [5,8]. The ROI was kept as large as possible to overcome the problem of heterogeneity. The average of signal intensities in two or three ROIs was taken for tumors where heterogeneity could not be addressed by a large ROI alone. In the present study, to provide objectivity, the TCTI ratio was used. A significant correlation was observed between the TCTI ratio and tumor consistency ($p = 0.036$). The TCTI was the most clinically significant option indicated in the present series for distinguishing between firm and soft meningiomas. This parameter also accounted for variations in T2 values in different subjects, as the own tissue acted as a reference.

The majority of studies that identified a link between consistency and conventional MRI have not provided measures of diagnostic accuracy, and do not seem to be useful in everyday clinical practice [9,12]. In the present series, the diagnostic performance of predictors with significant correlation with the consistency of meningioma was calculated. The best predictor in terms of diagnostic accuracy has been the TCTI ratio. Our results are similar to those of Smith et al. [13], where a single cut-off TCTI value of 1.41 for soft versus firm tumors was found to be 81.9% sensitive and 84.8% specific.

Our study did not reveal any significant correlation between the consistency of meningiomas and FA, MD, AD, and RD. Kashimura et al., however, discovered that the FA values of hard tumors were substantially greater than those of soft tumors ($p = 0.0003$) [6].

Okmura et al. found a significant difference in MTR between soft and hard tumors, although their study also included other tumors in addition to meningiomas. The MTR value for brain tumors was significantly less when compared to unaffected normal brain tissue ($p<0.05$). The MTR for meningioma was higher than that for other brain tumors ($p<0.05$). Within meningiomas, the MTR for the fibrous type was higher compared to the meningothelial type, but statistical significance could not be established [14]. However, the present study did not demonstrate any significant correlation between MTR and the consistency of meningiomas.

The key factors influencing signal intensities of the various meningioma subtypes are believed to be tumor cellularity, water content, and fibrous content [15]. The hardness of meningiomas is attributed to their high fiber content, according to several researchers, and histological appearance is one of the elements influencing tumor consistency [4,5]. However, Yamaguchi et al. documented no significant link between histological findings and the consistency of meningiomas [10]. In the present series, the consistency of various histologic subtypes correlated significantly with consistency ($p = 0.03$). All three angiomatous meningiomas were reported to have soft consistency, while all six fibroblastic meningiomas were noted to have firm consistency intraoperatively. The presence of psammoma bodies was correlated independently with tumor consistency. Although the correlation was not statistically significant, all 5 tumors reported to have psammoma bodies were firm, and none of the meningiomas with psammoma bodies had a soft consistency. This indicates that the relationship may indeed be significant but could not be established statistically due to insufficient power resulting from the small sample size. Over 75% of the cases studied by Elster et al. showed a good correlation between T2WI characteristics and histopathologic results [16]. Although histologic subtypes may appear differently on an MRI, Demaerel et al. suggested that the differences are insufficient to make a histologic diagnosis [17]. Our study showed a significant correlation between T2 signal intensity and histologic subtype ($p = 0.049$). All angiomatous types had T2 isointense signal intensity, while none of the fibroblastic types exhibited hyperintense signals on T2. The mixed signal intensity, which was iso and hypointense, had the largest proportion of fibroblastic types.

Kashimura et al. found that in comparison to meningothelial meningioma, fibroblastic meningioma had considerably higher FA values ($p=0.002$) [6]. In the present series, the mean (SD) FA value of fibroblastic meningioma was 0.30 (0.07), which was significantly higher compared to the meningothelial group, which had a value of 0.18 (0.10) ($p=0.05$). This may be because the fibrous component in fibroblastic meningiomas offers more resistance to diffusion in the direction perpendicular to the fibrous component, thus giving directionality to diffusion. The mean (SD) FA value of transitional meningioma was 0.28 (0.11), which, as expected, turned out to be intermediate, as it is a combination of both fibroblastic and meningothelial types [18].

Similar to our results, Okmura et al. also found that the MTR for fibrous-type meningiomas was higher compared to meningothelial-type meningiomas, but statistical significance could not be established for this finding [14]. This may be related to the higher collagen content in fibroblastic meningiomas.

The strength of this study is the participation of experienced neurosurgeons, radiologists, and pathologists. Objective parameters were included so that the interpretation could be reproduced. The application of the TCTI ratio improves objectivity and generalizability while reducing scanner and patient variability. This study is also the first study to consider the correlation between the consistency of meningiomas and DTI parameters other than fractional anisotropy, as well as to study the consistency of meningiomas in relation to their histopathologic subtypes.

The limitations of the present study include its limited sample size and interobserver bias among neurosurgeons in some cases where the CUSA score could not be assessed due to the inoperability of the CUSA for a period during the study because of equipment failure. Another limitation was that it was not a blinded study.

5. Conclusion

The consistency of the tumor is an important variable that affects the surgical plan and patient counseling. The neurosurgeon benefits significantly from knowing the tumor consistency prior to surgery while preparing for surgical methods. Prior knowledge of tumor consistency helps the surgeon anticipate difficulties in total tumor removal. This, in turn, influences the duration of surgery and the effectiveness of using tools, like CUSA.

Preoperative characterization of certain histopathological aspects of intracranial meningiomas may be greatly aided by MRI findings. There was a significant correlation between histopathological type and fractional anisotropy, MTR, and T2 signal intensity, as well as between radial diffusivity and fractional anisotropy with the presence of psammoma bodies. Although MRI is by no means a replacement for pathological analysis, multiparametric MRI may have some predictive utility in terms of the histology of meningiomas.

Ethical Considerations

Compliance with ethical guidelines:

The study was approved by the institutional review board and Institute Ethics Committee (No. BREC/Th/20/Radiodiag/09; dated 01.04.2021) and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. The article was extracted from a thesis defended at Pandit Bhagwat Dayal Sharma University of Health Sciences, Rohtak, Haryana, India. Written informed consent was obtained from the patients prior to the examination.

Funding:

No funding was received for this study.

Authors' contributions:

All authors contributed equally in performing all stages of the study.

Conflict of interest:

The authors reported no conflicts of interests.

Acknowledgements:

None.

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