Texture Analysis of Standard Magnetic Resonance Images to Predict Response to Gamma Knife Radiosurgery in Vestibular Schwannomas

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■ PURPOSE: **To search for texture features of routine magnetic resonance imaging to predict tumor volume reduction and transient versus permanent tumor progression of vestibular schwannomas treated by Gamma Knife stereotactic radiosurgery.**

■ MATERIALS AND METHODS: **Included were 23 patients with vestibular schwannomas treated in our center and followed over a period of 23.7–80.3 months (mean 42.7). Magnetic resonance imaging was performed on a 3-Tesla scanner and included T1-weighted images with and without contrast enhancement, T2-weighted, and fluid-attenuated inversion recovery images. Volumetric results were followed longitudinally over time and correlated to texture features as mean, minimum, maximum, standard deviation, skewness, and kurtosis of normalized signals taken from regions of interest covering the total tumor volume.**

■ RESULTS: **In total, 14 tumors showed early progression during the first 5–18 months (2 cases permanent, 12 cases transient), whereas 9 tumors regressed immediately after SRS. Kurtosis of T2-weighted image intensity values turned out to predict progression best with a sensitivity and specificity of 71% and 78%. From all texture feature parameters, only the minimum of the normalized T2-weighted image intensity values correlated significantly to the final reduction of tumor volume per month (correlation coefficient = −0.634, $P < 0.05$, corrected for false discovery rate).**

■ CONCLUSIONS: **Texture feature analysis helps to predict permanent versus transient enlargement and final volume reduction of schwannomas after SRS. Thus, alternative treatment strategies might be considered, mainly in large tumors, where further clinical deterioration cannot be excluded. To confirm these results, a prospective study including more cases and a longer follow-up period is necessary.**

INTRODUCTION

In contrast to other benign intracranial tumors like meningiomas or pituitary adenomas, approximately one half of all vestibular schwannomas do not start to regress immediately after Gamma Knife stereotactic radiosurgery (GKRS) treatment but show a transient enlargement during the following 1–2 years, until they eventually regress or continue to grow.[1] A transient enlargement of >10% of the original volume has been defined as "pseudo-progression."[2]

Due to transient or persistent enlargement, additional clinical deficits may occur that require further procedures, such as long-lasting treatment with steroids or even operation in 2%–14% of cases.[3-6] Because of these numbers, it seems justified to look for texture features before GKRS that could prognosticate further tumor enlargement, be it pseudo- or true progression. Larger tumor volume, lower radiation dose, and solid tumor type have been described as parameters predictive for tumor enlargement.[7,8]

Key words
- Magnetic resonance imaging
- Radiosurgery
- Texture analysis
- Vestibular schwannoma

Abbreviations and Acronyms
CC: Correlation coefficient
FDR: False discovery rate
FLAIR: Fluid-attenuated inversion recovery
FU: Follow-up
GKRS: Gamma knife stereotactic radiosurgery
MRI: Magnetic resonance imaging
TE: Echo time
TR: Repetition time

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However, other authors have not observed a significant difference in the further development between cystic and solid schwannomas.[9]

As far as magnetic resonance imaging (MRI) is concerned, some texture features of diffusion tensor imaging could be identified as predictive values in meningiomas.[10] In schwannomas, however, reported results so far are contradictory. No significant correlation between volume change and tumor enhancement has been reported by Nakamura et al.,[11] whereas Schneider et al.[12] found larger enhancing tumor areas in nonresponders. In accordance with the better response of cystic tumors in their group, diffusion-weighted images showed greater pre- and post-treatment apparent diffusion coefficient maxima in responders.[13,14]

Using a similar type of first-level texture recognition analysis as applied in meningiomas,[15] we retrospectively looked for texture features in a group of patients treated in our institution by GKRS that might predict tumor response more reliably than the degree of enhancement or cystic appearance. We deliberately confined the analysis to images measured during standard MRI examinations, because advanced techniques are usually not applied in most GKRS centers.

MATERIAL AND METHODS

This study was approved by the institutional review board at our institution and informed consent was obtained from all individual participants included in the study.

Patients and Schwannomas

Included were 23 patients, 11 male and 12 female, aged between 8.7 and 75.3 years, treated at our Gamma Knife center for acoustic schwannomas (Table 1). All patients presented with unilateral sporadic schwannomas. Pretreatment tumor volume ranged from 0.2 to 17.4 cm^3 (mean: 8.02 cm^3), and Koos grading from 1 (1 case), 2 (1 case), and 3 (5 cases) to 4 (16 cases). Six schwannomas had been operated before GKRS, and in 2 patients, shunts had been applied to treat ventricular congestion.

As criteria of inclusion, MRI examinations before GKRS and at least 1 "early" follow-up (FU) study within an interval of 5–18 months as well as at least 1 "final" FU study thereafter had to be available. The aforementioned limited time interval was chosen to cover a period in which the maxima of pseudo-progression could be expected. Total FU time was considerably longer and lasted up to 80.3 months, with a mean of 42.7 months. Data were evaluated in relation to volume changes per month as measured on scans from the "early" and "final" FU.

Gamma Knife Treatment

GKRS was performed on a Leksell Gamma Knife unit (Model 4C; Elekta, Stockholm, Sweden). The treatment was planned on a Leksell GammaPlan workstation (Version 10.1; Elekta) by carefully avoiding undue radiation to critical structures like the brainstem or the cochlea, keeping the coverage index as high as possible (mean: 93.2%). The margin dose was 11–14 Gy (mean: 12.2 Gy) applied in a single session, except for one case treated by hypofractionated GKRS (3 × 5 Gy, corresponding to a single fraction equivalent dose of 9.4 Gy, applying an alpha/beta ratio of 2.4 Gy).[16]

Table 1. Patients, Tumor Volume, and Type, Margin Dose, Length of Last Follow-Up, and Change of Volume per Month Measured at an Interval of 6–24 Months and at Last Follow-Up

Characteristics	Values
Number of patients	23
Age, years	51.6 (8.7–75.3)
Tumor volume, cm^3	8.02 (0.2–17.4)
Tumor type (solid/micro/macrocystic)	4:8:11
Margin dose, Gy	12.2 (11.0–14.0)
Delay to last follow-up, months	42.7 (23.7–80.3)
Volume change per month as measured between 5 and 18 months	+1.70 ± 5.34%
Volume change per month at last follow-up	−0.95 ± 1.14%

Minimum and maximum values are stated in parentheses.

Magnetic Resonance Imaging

MRI was performed on a 3-Tesla scanner (Achieva; Philips, Eindhoven, Netherlands). The following sequences were applied: 1) 3-dimensional T1 magnetization-prepared rapid acquisition with gradient echo, repetition time (TR)/echo time (TE) 6.8/3.2 milliseconds, TI (TFE prepulse) 900 milliseconds, flip angle 8°, measured voxel size 0.6*0.6*1.0 mm, before and after intravenous injection of contrast medium. 2) T2, TR/TE 2050/80 milliseconds, 25 transversal slices, thickness 5 mm, matrix 512 × 512 (8 cases) or TR/TE 3693.8/80 milliseconds, 150 transversal slices, thickness 1 mm, matrix 512 × 512 (13 cases). 3) Fluid-attenuated inversion recovery (FLAIR) TR/TE/TI 11,000/120/2800 milliseconds, 90 transversal slices, thickness 2 mm, matrix 512 × 512.

Classification of Schwannomas

According to the criteria published by Bowden et al.,[2] tumors were classified as solid, micro-, and macrocystic.

Postprocessing

In all 23 patients, tumor volumes were outlined and measured from 3-dimensional T1-weighted contrast-enhanced images on the Leksell GammaPlan workstation and transferred to T2-weighted, FLAIR and T1-weighted images without enhancement. In 1 patient, FLAIR images and in 2 patients, nonenhanced T1-weighted images were not available before GKRS, and for evaluation of these texture features, only 23 and 22 patients, respectively, were included.

MRIcro software (www.cabiatl.com/mricro) was used to outline regions of interest interactively covering the whole tumor corresponding Signal intensity values were measured and related to the means of white matter, taken from 3 different regions of interest placed into the genu, splenium of the corpus callosum of the same images. From these data, the following texture features were calculated using the basic functionality of Excel (Microsoft, Redmond, Washington, USA): mean value, standard deviation,

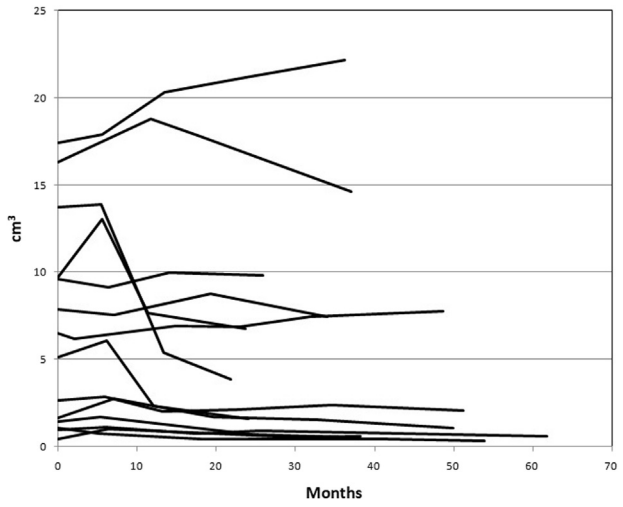

Figure 1. Volume changes of vestibular schwannomas after gamma knife stereotactic radiosurgery.

minimum and maximum, skewness and kurtosis, and 2.5 and 97.5 percentile.

Tumor volume change per month was measured from enhanced T1-weighted images and calculated for 2 periods: 1) from time of GKRS to "early" FU between 5 and 18 months and 2) from time of GKRS to final FU. Using the functionality of the statistical package SPSS 15.0 (SPSS, Inc., Chicago, Illinois, USA), we performed a partial correlation analysis correlating the change of tumor volume after GKRS per month to the various texture features, correcting for the delay time (interval between GKRS and FU) and the margin dose, which were entered as control variables. We also conducted a linear regression analysis with tumor volume change per month as a dependent variable and the aforementioned texture feature values as independent variables to look at which value or combination of values accounts best for the variance of volume change. Because multiple datasets were included, the calculation for significance was adjusted for multiple comparisons by false detection rate correction (FDR, www.sdmproject.com/utilities/?show=FDR; Benjamini and Hochberg[17]). The level of significance was set to 95%.

To calculate sensitivity and specificity of texture feature values to predict tumor progression, cases were separated into "progressors" and "regressors," and the difference of texture features between both groups was compared by t test. From those values showing the greatest difference, the upper and lower quartiles were calculated. Using the lower quartile of the "progressors" as a separator, we calculated sensitivity, specificity, and positive and negative predictive values (http://vassarstats.net/clin2.html). A comparison of texture feature values between tumor types (solid vs. microcystic vs. macrocystic) was also done by t test.

RESULTS

Change of Tumor Volume

According to T1-weighted images measured before GKRS, tumor volume ranged from 0.2 to 17.4 cm^3 with a mean of 8.02 cm^3. After

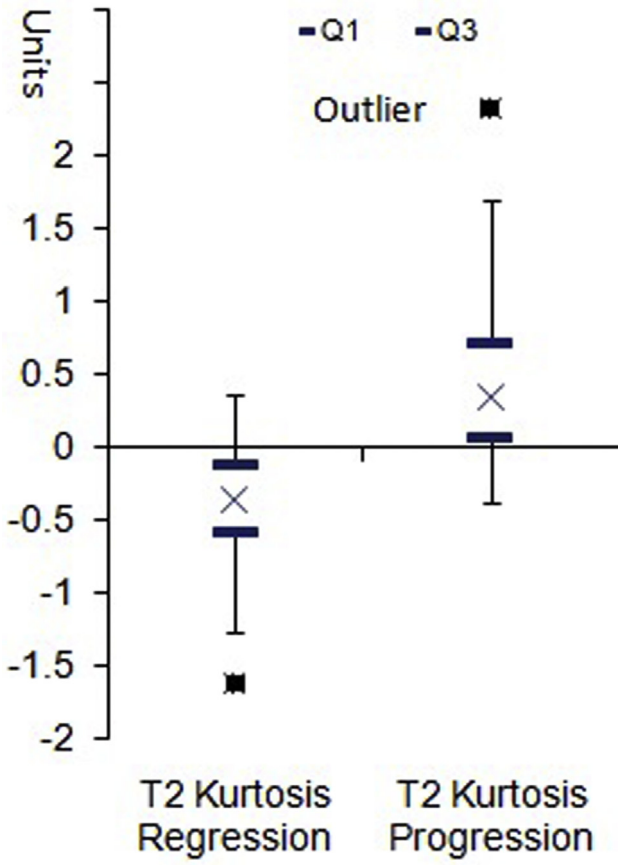

Figure 2. Box plot of kurtosis of relative T2 signal values of vestibular schwannomas, differentiated into cases with immediate regression and cases with transient or permanent enlargement, showing mean value (*cross*), quartiles (*bar*), and outliers (*square*).

GKRS, 9 of 23 tumors showed a constant regression of volume, 2 tumors (cases 8 and 14) constantly progressed, and 12 tumors showed transient progression, peaking within an interval of 5 and 18 months, but finally regressed as well (**Figure 1**). In 2 cases of the latter group, the final regression was incomplete and did not come back to the original level. They nevertheless were classified as "transient progressors" because of final volume regression. During the "early" period of 5–18 months, the mean tumor volume of all cases increased per month for 1.7 ± 5.34%, whereas final measurements done after an FU of more than 20 months (mean: 41.8 months) showed a mean volume regression of 0.95 ± 1.14% per month. Those 12 tumors with transient progression during the first 5–18 months showed an initial increase of volume of 0.95 ± 0.99 cm^3 or 29% and regressed thereafter. In the 2 cases with continuous progression, volumes increased from 6.5 to 7.8 cm^3 during 48.7 months and from 17.4 to 22.2 cm^3 during 36.3 months.

Correlation of Tumor Types to Volume Change

Although there was no significant correlation to transient or final change of tumor volume after GKRS, we saw a trend to a greater

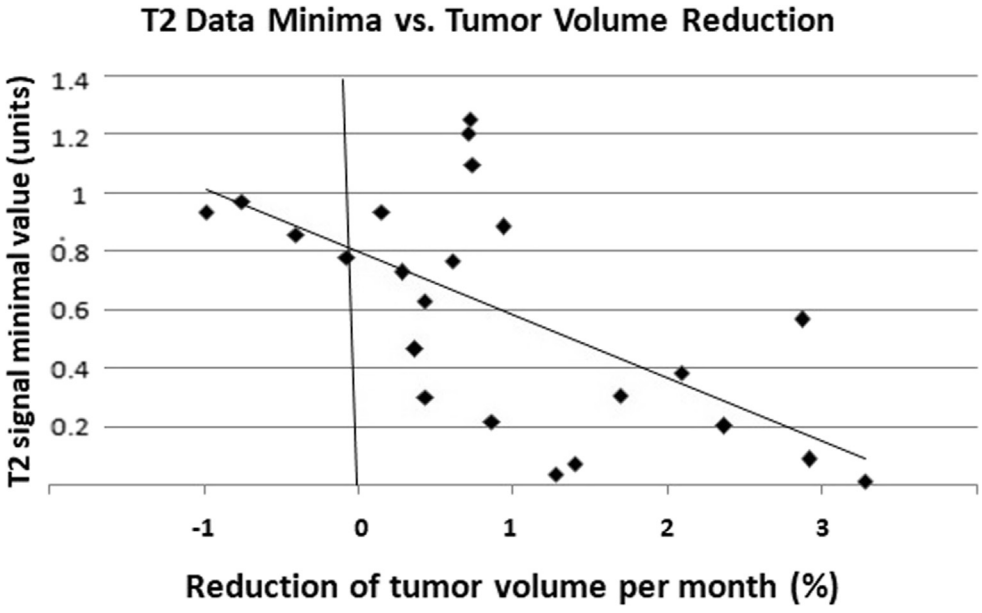

Figure 3. Final tumor volume reduction per month correlates significantly to the minima of T2-weighted signal intensities ($P < 0.05$, false discovery rate corrected).

final regression rate in cystic growths. Whereas the solid tumors finally regressed for 0.9% and the microcystic ones for 0.4% per month, final regression in the macrocystic tumors was faster (1.5% per month), and the difference between macro- and microcystic types reached significance ($P = 0.032$). With regard to early volume change, we saw progression in cystic tumors (1.5% per month in the macro- and 3.2% per month in the microcystic types), whereas the solid ones regressed for 1% per month. These differences, however, were not significant. Using the presence of intratumoral cysts of any kind as the criterion to predict subsequent tumor growth, the resulting sensitivity and specificity amounts to 63.2% and 50.0%, respectively.

Correlation of Texture Features to Change of Volume During the First 18 Months

After FDR correction, none of the texture features correlated significantly with the volume change at FU during the first 18 months, but the minimum of contrast-enhanced T1 showed the highest value (correlation coefficient [CC] = −0.423, $P > 0.05$). Linear regression analysis only kept this value as an independent variable to account for the variance of early regression with an R^2 of 0.227. Within this group of 14 "progressors," tumor volume increased permanently in 2 patients, and these cases 2 showed a significantly greater mean of signal values of enhanced T1 weighted images (2.513 vs. 1.979 units, $P = 0.005$). All other differences were not significant.

The comparison of texture features between the group of 14 "progressors" and the 9 "regressors" did not show significant differences, but a trend for the feature "kurtosis" of T2 ($P = 0.169$ after FDR correction) being positive in the progressor group ($k = 0.452 \pm 0.671$) and negative in the regressor group ($k = -0.413 \pm 0.590$). Using the lower quartile of T2 kurtosis from the "progressors" $k = 0.060$ (Figure 2) as separating value, we achieved a sensitivity to predict any kind of progression, transient or permanent, of 71% and a specificity of 78% within the complete group, resulting in a positive predictive value of 86% and a negative predictive value of 59%.

Correlation of Texture Features to Change of Volume at Last FU

After correction for length of FU and for radiation dose, the greatest CC between imaging texture feature values and reduction of tumor volume per month measured at final FU turned out to be the minimum of relative T2-weighted image intensity values (CC = −0.634) followed by the standard deviation of T2 signal values (CC = 0.566, Figures 3 and 4, Table 2). The first CC reached statistical significance ($P = 0.042$, FDR corrected). Linear regression analysis using final tumor reduction as dependent and other parameters and features as tumor type, radiation dose, length of final and texture features derived from imaging as independent variables, gave a similar result: only minimum T2 was included into the analysis accounting for 40.2% of the variance of final volume change. All other parameters were excluded. Regression analysis calculates the causal relationship between the dependent and independent variables, in this study between volume change and the MRI parameters, and excludes those parameters that do not contribute significantly to explain the variance of the volume change.

DISCUSSION

In compliance with the literature findings,[18,19] GKRS was successful in 91% of our cases, resulting in a final tumor control in 21

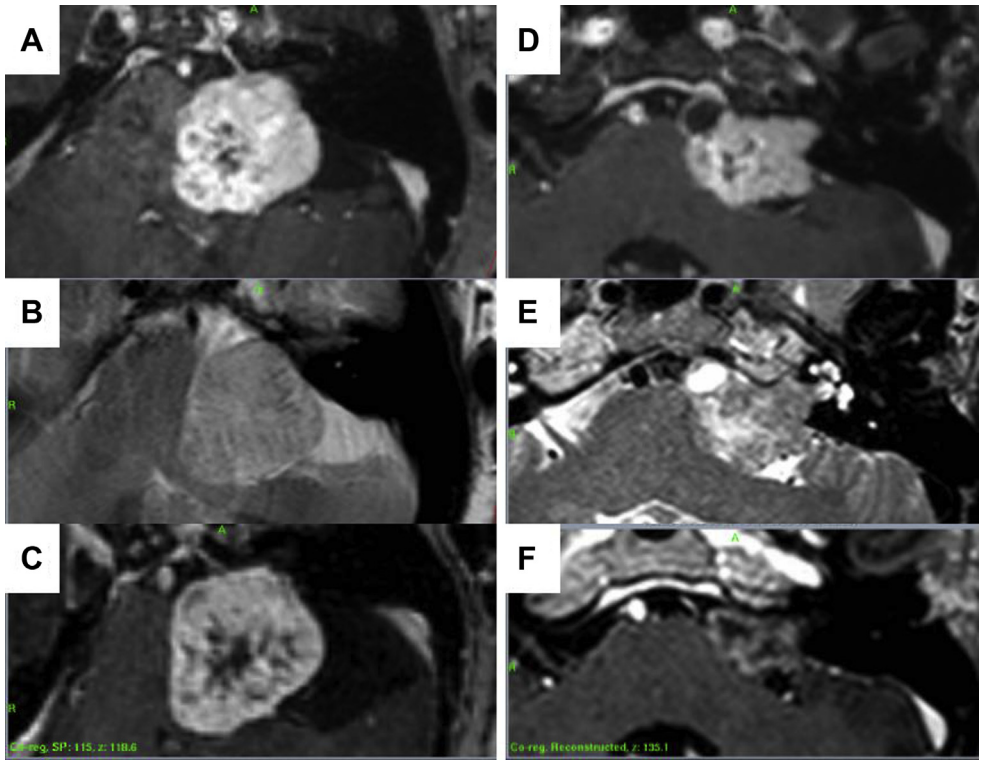

Figure 4. Examples of conventional magnetic resonance imaging of 2 schwannomas. (**A**–**C**) Schwannoma with volume progression of 0.75% per month, presenting a low normalized standard deviation (SD) of T2: 0.124. Gamma knife stereotactic radiosurgery, in this case, was indicated because of advanced age and general bad condition. Unfortunately, the tumor continued to grow and finally had to be operated. The progression could have been predicted by the kurtosis of the T2 image intensity values, which was well above the separating value of k = 0.060. However, this result of our study was unknown to us at the time of decision making. (**A**) Contrast-enhanced (CE)-T1-weighted image before stereotactic radiosurgery (SRS). (**B**) T2-weighted image before SRS. (**C**) CE-T1-weighted image 36.3 months after SRS. (**D**–**F**) Schwannoma with significant volume regression of 2.87% per month, presenting a high normalized SD of T2: 0.505. (**D**) CE-T1-weighted image before SRS. (**E**) T2-weighted image before SRS. (**F**) CE-T1-weighted image 24.1 months after SRS.

of 23 cases, whereas 2 schwannomas progressed. These 2 patients showed a significantly greater signal of tumor tissue after injection of contrast medium compared with the 12 transiently enlarging tumors. However, because of the small group size, we are reluctant to recommend this finding as a prognostic parameter.

A transient increase of volume after GKRS was seen in 61% (12 of 23) cases, with a mean enlargement of 29% of volume as compared with the status before GKRS. This amount, as well as the frequency of transient progression, is well within the range of 20%–75% and 10%–74%, respectively, reported previously.[20] Although the mean volume increase was less than 1 cm,[3] in one case it amounted to 3.34 cm^3 within 6 months and thus got into the range of the 2 continuously enlarging schwannomas. Because this patient did not develop additional deficits, we followed a conservative regime, because late volume reductions after GKRS may be seen after 3 years or more.[21,22]

The pathologic background of pseudo-progression is not precisely known. Inflammation, radiation-induced tumor necrosis, and chronic intratumoral hemorrhage have been suggested as potential mechanisms,[23] but why this only occurs in a subset of treated tumors is still not known.

Transient or permanent progressive enlargement of initially large schwannomas may result in additional compression of the cranial nerves or of the brainstem,[24] and for treatment planning, it could be helpful to predict this possibility. According to our results, the texture features "kurtosis" of the relative T2 signal of MRI scans served best to prognosticate regression or progression during the first 18 months. Kurtosis is a measure of the combined weight of a distribution's tails relative to the center of the distribution. If a dataset has a positive kurtosis, it has more outlier data in the tails of the histogram than the normal distribution, and fewer outliers in case of a negative

Table 2. Imaging Parameters before GKRS and Correlation to Change of Tumor Volume per Month at Final Follow-Up, Corrected for Delay to Follow-Up and Radiation Dose Applied at GKRS

	Mean	SD	Minimum	Maximum	Kurtosis	Skewness	2.5 Perc.	97.5 Perc.
T2; CC	1.728 ± 0.380; 0.060	0.321 ± 0.150; 0.566	0.594 ± 0.392; −0.634*	2.754 ± 0.817; 0.460	0.114 ± 0.761; −0.253	0.018 ± 0.450; 0.125	1.499 ± 0.356; −0.199	1.954 ± 0.463; 0.216
FLAIR; CC	1.602 ± 0.428; 0.24493	0.279 ± 0.108; 0.532	0.629 ± 0.301; −0.395	2.464 ± 0.661; 0.395	0.058 ± 0.499; −0.175	−0.200 ± 0.407; −0.192	1.417 ± 0.400; 0.154	1.800 ± 0.477; 0.319
T1 + CM; CC	1.973 ± 0.351; −0.299	0.423 ± 0.195; 0.307	0.435 ± 0.208; −0.473	3.317 ± 0.753; 0.099	0.826 ± 1.320; −0.222	−0.509 ± 0.480; 0.157	1.706 ± 0.420; −0.377	2.270 ± 0.390; −0.145
T1; CC	0.606 ± 0.053; −0.134	0.085 ± 0.042; 0.193	0.267 ± 0.075; −0.298	0.975 ± 0.325; 0.063	0.575 ± 0.813; 0.027	−0.024 ± 0.470; 0.173	0.551 ± 0.044; −0.314	0.659 ± 0.064; −0.040

GKRS, Gamma Knife stereotactic radiosurgery; SD, standard deviation; FLAIR, fluid-attenuated inversion recovery; CC, correlation coefficient; CM, contrast medium.
*Significant correlation ($P \leq 0.05$, false discovery rate corrected).

kurtosis. Using k = 0.060 as separating value as described previously, sensitivity and specificity and predictive values of this parameter are within acceptable limits and definitively greater than the corresponding values derived from the cystic properties of the growth. However, it does not differentiate between transient and permanent progression.

The greater kurtosis of T2 in progressing tumors could mean that these were predominantly Antoni B types with large cysts.[25] In fact, there were more macrocystic growths in the group of progressors than in the regressors' group (8:6 vs. 3:6). However, a significant correlation between kurtosis of relative T2 signal and tumor type could not be demonstrated, which might be due to the fact, that the histograms of cystic types demonstrated more than a single peak of signal values.

Whereas a greater rate of early progression in solid schwannomas has been reported by Wu et al.[14] and Kim et al.,[26] others found transient tumor enlargement more often in the cystic types, mainly of the cysts themselves, followed by a greater tumor reduction rate.[11,27,28] Frisch et al.[9] did not observe any predictive factor for important cyst enlargement in 4 of 20 cystic schwannomas, and 2 of them finally regressed. In several other series, no clinical or radiosurgical dosimetric parameters were found to be significantly associated with early tumor enlargement.[20,23,29]

As far as the final results of GKRS in schwannomas are concerned, the only texture feature reaching significance after correction for length of FU and radiation dose was the correlation between final tumor volume reduction and the minimum of relative T2-weighted image intensity values within the schwannoma. Linear regression analysis pointed to a similar direction. Cystic tumors usually show greater T2-weighted image intensity values and correspondingly greater T2 minima as well as an inhomogeneous signal distribution.[25]

Whereas the correlation between volume change and the standard deviation of T2-weighted image intensity values fits into this pattern, the aforementioned correlation of the T2 minima was negative, suggesting that cystic schwannomas are the ones that shrink at a lower rate. This result is different from the (nonsignificant) finding of our study that cystic schwannomas finally showed a greater rate of volume reduction per month. A similar greater rate of final regression in cystic schwannomas has been reported by Nagano et al.[24] and Frisch et al.[9] As found in our series, the macrocystic types were the ones to regress most.[2]

This apparent discrepancy of the positive correlation between tumor regression and standard deviation of T2 signal and the negative one between regression and T2 minimum may be explained as follows: In our series, macrocystic schwannomas, which had the greatest reduction rate, presented mean minima of relative T2-weighted image intensity values considerably lower than those of solid or microcystic tumors (0.454 vs. 0.792 and 0.720 units), whereas the mean maxima were greatest in the macrocystic group, followed by the microcystic and the solid tumors (3.208 vs. 2.405 and 1.952 units). This finding corresponds to the variation of the standard deviation of T2-weighted image intensity values, which was greatest in the macrocystic growths, and might be due to the higher tissue inhomogeneity of this type of schwannomas.

CONCLUSIONS

Results of the present study confirm that cystic schwannomas, mainly the macrocystic ones, respond more favorable to GKRS than the solid types. Texture feature analysis helps to predict permanent versus transient enlargement and final volume reduction of schwannomas after stereotactic radiosurgery. To predict transient volume enlargement after GKRS, the parameter kurtosis of relative T2-weighted image intensity values might be used with an acceptable sensitivity and specificity to consider alternative treatment strategies, mainly in large growths, where further clinical deterioration might be possible. From all texture feature parameters, only the minimum of the normalized T2-weighted image intensity values correlated significantly to the final reduction of tumor volume per month. To confirm these results and to work out predictive texture features to differentiate between pseudoprogression and permanent enlargement, a prospective study including more cases and a longer FU period is necessary.

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