The efficacy of radiosurgery is usually confirmed by posttreatment contrast-enhanced MR imaging evaluating the development of tumor size and changes in contrast agent uptake. There have been ongoing discussions about the clinical relevance of contrast enhancement of the central tumor portion following radiosurgery. So far, for VS, 3 different types of MR imaging appearance have been described with respect to contrast agent uptake: homogeneous (50–60% of all VS), heterogeneous (30–40%), and cystic (5–15%) (Fig. 1). Especially in heterogeneous tumors, hypointense areas with lack of contrast enhancement may not be consistent with intraoperative "necrotic tumor areas." Until now, however, correlation between contrast enhancement and timing of image acquisition in nontreated VS has not been analyzed systematically. The authors undertook this study to investigate changes in contrast enhancement with respect to latency of image acquisition after contrast agent administration.

**Methods.** The dynamics of contrast medium uptake were evaluated with T1-weighted VIBE MR imaging sequences performed immediately and 1.5, 3.5, 4.5, 9.5, and 11.5 minutes after administration of single dose of Gd in 21 patients with nontreated medium- to large-sized VSs. Signal-to-noise (SNR) and contrast-to-noise ratio (CNR) of tumors were evaluated, and volumes of central nonenhancing areas (NEAs) were determined.

**Results.** The interior appearance of the tumors changed considerably over time. The NEA significantly diminished in size ($p < 0.0001$, Friedman test) and almost completely disappeared in all but 2 patients. Compared to images at 1.5 minutes, NEA volumes decreased to a median of 36% at 3.5 minutes and 34% at 4.5 minutes, showing smaller changes after that—9% at 9.5 minutes and 3% at 11.5 minutes. Tumor SNR and CNR increased over time. The maximum change in the median values for SNR and CNR were a 72% increase and 117% increase, respectively; both occurred at 1.5 minutes after Gd administration.

**Conclusions.** Contrast enhancement in VS MR imaging varies according to the duration of the delay between contrast agent administration and image acquisition. Postradiotherapy changes in contrast enhancement of VS can therefore not be attributed only to effective radiotherapy. So-called “loss of central contrast enhancement” may be falsely detected because of timing. A standardized protocol with defined timing of image acquisition may increase comparability of contrast uptake in VS. (DOI: 10.3171/2010.5.JNS10307)

**Object.** Efficacy of radiosurgery in vestibular schwannoma (VS) is usually documented by changes of tumor size and by loss of contrast enhancement in MR imaging within the central portion of the lesion. Until now, however, correlation between contrast enhancement and timing of image acquisition in nontreated VS has not been analyzed systematically. The authors undertook this study to investigate changes in contrast enhancement with respect to latency of image acquisition after contrast agent administration.

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SEQUENCES PERFORMED IMMEDIATELY AND 1.5, 3.5, 4.5, 9.5, AND 11.5 MINUTES AFTER ADMINISTRATION OF A SINGLE DOSE OF Gd (0.2 ml/kg, 1 ml/sec, MEDRAD Inc.) IN 21 PATIENTS (11 WOMEN, 10 MEN; MEAN AGE 45 YEARS, RANGE 24–68 YEARS), SUFFERING FROM MEDIUM- TO LARGE-SIZED VS (MEAN DIAMETER 24 MM, RANGE DIAMETER 10–48 MM). WITH RESPECT TO RADIOLOGICAL CLASSIFICATION IN HOMOGENEOUS, HETEROGENEOUS, AND CYSTIC TUMORS, THE MOST REPRESENTATIVE IMAGES OF THE DYNAMIC SERIES WERE USED (T1-WEIGHTED VIBE, TR 9.82 MSEC, TE 4.92 MSEC, SL 1 MM, FOV 130 × 160 MM, MATRIX 135 × 256 PIXELS, 12° FA, 135 PHASE-ENCODING STEPS).

An ROI analysis was performed as described by Wintersperger et al.33 the VS volume was manually segmented in the last image of the series with clearly delineated tumor. This volume was then transferred to all other image series, which were coregistered to correct minor changes due to patient movement (MIPAV software, Center for Information Technology). Segmented volume was used as ROI_{tumor}. In addition, a homogeneous area of enhancement within normal brain was manually defined (ROI_{brain}), as well as an artifact-free region within the surrounding air (ROI_{air}), as large as the extent of the images permitted. Signal-to-noise (SNR) and contrast-to-noise ratios (CNR) were calculated according to the following formulas:

\[
\text{SNR}_{\text{brain},t} = \frac{S_{\text{brain},t}}{S_{\text{air},t}}
\]

\[
\text{SNR}_{\text{tumor},t} = \frac{S_{\text{tumor},t}}{S_{\text{air},t}}
\]

\[
\text{CNR} = \frac{(S_{\text{tumor},t} - S_{\text{brain},t})}{S_{\text{air},t}}
\]

where \(S_{\text{tumor},t}\) is the average signal intensity in ROI_{tumor}, \(S_{\text{brain},t}\) the average brain signal intensity in ROI_{brain}, and \(S_{\text{air},t}\) the standard deviation of the background signal in ROI_{air} at time point t.

To objectively estimate the volume of central areas without signal enhancement at each time point, areas within the tumor with CNR values below 5 were identified. The threshold value of 5 corresponds to the lower limit of visually obvious contrasts,1 that is, voxels with CNR values below 5 are not discernible from normal brain tissue without contrast agent uptake.

Influence of image acquisition time on SNR, CNR, and size of areas without signal enhancement was statistically analyzed using the Friedman test; differences between successive images were tested using the Wilcoxon rank sum test (MATLAB software, The MathWorks, Inc.).

RESULTS

In the investigated sample of patients, all 3 subtypes—homogenous, heterogeneous, and cystic—were present: 6 patients (28.5%) presented with homogeneous tumors, 13 (62%) with heterogeneous, and 2 (9.5%) with cystic tumors, but subtype did not have any noticeable influence on the contrast agent uptake behavior.

Time of image acquisition after contrast agent administration did not have any detectable influence on the extent of the enhanced tumor volume. Figures 2 and 3 show 2 examples.

VOLUME OF NONENHANCING AREAS

In contrast to the stability of overall tumor size, interior appearance changed considerably over time. At early time points, low SNR and CNR allowed only limited evaluation of NEAs. Due to incomplete contrast agent uptake at this stage, a large proportion of the tumor did not reach a minimum CNR of 5 and was not distinguishable from normal nonenhancing brain tissue (expressed by large volume values in Table 1 and Fig. 4). At later time points, contrast agent enhancement allowed clear identification of NEAs, however, the appearance of these areas was not stable. In all patients, volumes of these tumor portions decreased; the median NEA at the last time point was only 11% of that in the images obtained 1.5 minutes after contrast agent administration. Compared to images at 1.5 minutes, the first time point after the initial contrast agent uptake, NEA volumes decreased considerably to median values of 36% at 3.5 minutes and 34% at 4.5 minutes. Further decrease was still observed at 9.5 and 11.5 minutes, when the median NEA volumes had reached, respectively, 9% and 3% of the NEA volumes at 1.5 minutes.

Statistical analysis showed a significant influence of time of image acquisition on the extent of NEAs both when all time points were considered (p < 0.0001, Friedman test) and when analysis was constrained to the last 3 (p < 0.0001).
Fig. 2. Series of MR images showing a VS with strong changes in contrast enhancement over time. The images were obtained immediately (A) and 1.5 (B), 3.5 (C), 4.5 (D), 9.5 (E), and 11.5 (F) minutes after Gd administration. Note that the central NEAs of the tumor diminish in size and eventually disappear.

Fig. 3. Series of MR images showing a VS with only minor changes in contrast enhancement over time and minor interior inhomogeneities or central NEAs. The images were obtained immediately (A) and 1.5 (B), 3.5 (C), 4.5 (D), 9.5 (E), and 11.5 (F) minutes after Gd administration.
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Signal-to-Noise Ratio

The SNR values increased from a median value of 14.3 to a maximum of 34.3 at 11.5 minutes after Gd administration, and the largest median increase (72%) was found in the initial phase (up to 1.5 minutes after Gd administration). The difference between the values at 0 and 1.5 minutes was found to be significant ($p < 0.0001$, Wilcoxon rank sum test, 2-sided) and the difference between the values at 1.5 and 3.5 minutes reached a statistical level of a tendency ($p < 0.1$), while the remaining differences were not significantly different, when values of successive time points were compared (Fig. 5). The Friedman test showed a significant influence of time of image acquisition on SNR when all time points were considered ($p < 0.0001$), as well as when only the last 3 were considered ($p < 0.005$).

Contrast-to-Noise Ratio

The CNR values also increased over time from a median of 4.3 to a maximum of 34.3 at 11.5 minutes after Gd administration, and the largest median increase (117%) was seen at 1.5 minutes after Gd administration. The difference between the values at 0 and 1.5 minutes was found to be significant ($p < 0.0001$, Wilcoxon rank sum test, 2-sided) and the difference between the values at 1.5 and 3.5 minutes reached a statistical level of a tendency ($p < 0.05$), whereas the differences between sets of values obtained at subsequent successive time points were not. As for SNR, the Friedman test also showed a significant effect of time of image acquisition on CNR both when all time points ($p < 0.0001$) were considered and when only the last 3 were considered ($p < 0.005$).

Discussion

Since the introduction of the Gamma Knife for the treatment of VS,$^{19}$ there have been ongoing discussions about the criteria for tumor response. Posttreatment MR imaging evaluates tumor size and changes in contrast enhancement.$^{4,5,11,18,20,24}$ Central tumor hypointensity following radiosurgery has been reported by Selch et al.$^{31}$ in 67% of treated patients, by Chung et al.$^{5}$ in 69.5%, by Norén et al.$^{25}$ in 70%, by Bertalanffy et al.$^{2}$ in 78%, and by Pol-

### Table 1: Volumes of tumors and NEAs over time in 21 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Tumor Vol (mm³)</th>
<th>NEA Volume (mm³)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
<td>1.5 min</td>
</tr>
<tr>
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<td>21</td>
<td>843</td>
<td>261</td>
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</tbody>
</table>

* Values represent volumes of the tumors and of the nonenhancing areas (NEAs) of the tumors immediately after Gd administration (0 min) and 1.5, 3.5, 4.5, 9.5, and 11.5 minutes thereafter.
lock\textsuperscript{27} in 93%. The clinically relevant implication of this observation remains unclear, especially as Ganslandt et al.\textsuperscript{10} for example, described that histopathological examination of a previously irradiated tumor with hemorrhage into cystic VS showed no radiotherapy-induced necrosis.

We conducted the current study because there was a lack of systematic data about contrast agent uptake in VS. We found considerable variation of tumor contrast enhancement on MR imaging over time depending on the delay between contrast administration and image acquisition. Central hypointense tumor portions disappeared almost completely in all but 2 patients during the course of the MR imaging session. The increasing contrast enhancement in tumor areas that were initially nonenhancing could be a consequence of different perfusion and enhancement in tumor areas that were initially nonenhancing, due to economic considerations. Under these circumstances, it is important to know that contrast enhancement of VS generally varies in the first 4.5 minutes after Gd administration were only seen in one patient, major changes in contrast enhancement later than 4.5 minutes after Gd administration were only seen in one patient, suggesting higher validity of delayed image acquisition.

In our patient population, there was a relatively high percentage of heterogeneous tumors as compared with findings reported in the literature: 62% versus 30%–40%.\textsuperscript{3} This might be explained by the fact that we investigated medium- to large-sized tumors, in which heterogeneous tumor components are frequently found;\textsuperscript{3,4,6,11} thus, evaluation of smaller, more homogeneous tumors might be affected less by irregular contrast agent uptake.

Though in some follow-up series\textsuperscript{24} MR imaging does not start until at least 5 minutes after bolus injection of contrast agent, a standardized protocol is not established even in academic centers, and timing of data acquisition is frequently not reported.\textsuperscript{13,21,29} Furthermore, MR imaging follow-up examinations are often performed in nonacademic institutions, possibly resulting in much shorter time intervals, due to economic considerations. Under these circumstances, it is important to know that contrast enhancement of VS generally varies in the first 4.5 minutes after contrast agent administration. For treatment control, we recommend standardized protocol–based identical T1-weighted sequences and strict timing between contrast agent administration and image acquisition. Additional studies should verify this in irradiated VS.

**Conclusions**

As irregular contrast enhancement with central areas of signal hypointensity occurs in untreated VS, changes in irradiated VS should not necessarily be attributed to radiotherapy alone. So-called “necrotic tumor areas” may be falsely detected because of timing of image acquisition
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with respect to the administration of contrast medium. A standardized MR imaging protocol with identical timing of image acquisition may therefore increase comparability of contrast uptake in VS.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Strauss, Rachinger, Scheller. Analysis and interpretation of data: Rampp, Engelhorn. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Rampp.

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