Comparison of Brain Tumor Contrast-enhancement on T1-CUBE and 3D-SPGR Images

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Purpose: T1-Cube (GE HealthCare) is a relatively new 3-dimensional (3D) fast spin-echo (FSE)-based magnetic resonance (MR) imaging sequence that uses a variable flip angle to acquire gap-free volume scans. We compared the gadolinium enhancement characteristics of a heterogeneous population of brain tumors imaged by T1-Cube and then 3D fast spoiled gradient recall acquisition in steady state (3D FSPGR) 3-tesla MR imaging to identify the superior modality for specific diagnostic purposes.

Methods: We examined 61 lesions from 32 patients using the 2 sequences after administration of gadopentetic acid (Gd-DTPA; 0.1 mmol/kg). Two neuroradiologists independently measured each lesion twice using a region-of-interest (ROI) method. We measured the contrast-to-noise ratio (CNR), the difference in signal intensity (SI) between the tumor and normal white matter relative to the standard deviation (SD) of the SI within the lesion, for both post-contrast 3D FSPGR and post-contrast T1-Cube images of the same tumor and compared modality-specific CNRs for all tumors and in subgroups defined by tumor size, enhancement ratio, and histopathology.

Results: The mean CNR was significantly higher on T1-Cube images than 3D FSPGR images for the total tumor population (1.85 ± 0.97 versus 1.12 ± 1.05, \( P < 0.01 \)) and the histologic types, i.e., metastasis (\( P < 0.01 \)) and lymphoma (\( P < 0.05 \)). The difference in CNR was even larger for smaller tumors in the metastatic group (4.95 to 23.5 mm²) (\( P < 0.01 \)). In contrast, mean CNRs did not differ between modalities for high grade glioma and meningioma.

Conclusions: Gadolinium enhancement of brain tumors was generally higher when imaged by T1-Cube than 3D FSPGR, and T1-Cube with Gd enhancement may be superior to 3D FSPGR for detecting smaller metastatic tumors.

Keywords: brain tumor, contrast-enhanced magnetic resonance imaging (CE MRI), T1-Cube sequence, 3-dimensional fast spoiled gradient recall acquisition in steady state (3D FSPGR)

Introduction

Two-dimensional (2D) contrast-enhanced magnetic resonance imaging (CE MRI) using T1-weighted spin-echo (SE) or 3-dimensional (3D) gradient-echo (GRE) sequences is the most common imaging modality for detecting and evaluating brain tumors.1–3 Previous studies, however, reported better visualization of small tumors by thin 3D GRE images, such as 3D fast spoiled gradient recall acquisition in the steady state (3D FSPGR), than by conventional 2D T1-weighted SE images.1,4 Indeed, 3D T1-weighted GRE imaging with high spatial resolution can be advantageous for detecting small enhancing brain tumors because it minimizes...
partial volume effects.\textsuperscript{4–6} On the other hand, Furu-
tani’s group\textsuperscript{1} reported lower enhancement on 3D FSPGR images than conventional 2D T\textsubscript{1}-weighted SE images, even with 3T MR imaging, indicating that thin-slice CE 2D T\textsubscript{1}-weighted SE images may be preferable for the detection of smaller tumors and brain metastasis.

T\textsubscript{1}-Cube is a relatively new 3D T\textsubscript{1}-weighted fast spin-echo (FSE) sequence that uses a variable flip angle technique and higher echo train length to reduce acquisition time and specific absorption rate. This allows T\textsubscript{1}-Cube imaging to provide submillimeter, isotropic 3D data sets that can be reformatted into any plane to visualize even small and low-contrast lesions without partial-volume effects.\textsuperscript{7,8} In fact, the similar “sampling perfection with application-optimized contrasts by using different flip angle evolutions” (SPACE) sequence has proven advantageous for detecting brain metastasis compared with 3D T\textsubscript{1}-weighted GRE sequences.\textsuperscript{9,10} In this study, we compared post-contrast T\textsubscript{1}-Cube and 3D FSPGR images of the same brain tumors to identify advantages and limitations of these modalities for analysis of specific brain tumor subgroups defined by size, degree of enhancement, and histopathological type.

**Materials and Methods**

This study was approved by our institutional re-
view board and prospectively performed after ac-
quision of informed consent from all patients.

**Imaging protocols**

All MR examinations were performed using a 3T MR scanner (Discovery 750, GE HealthCare, Mil-
waukee, WI, USA) and standard 8-channel head coil. We obtained 3D FSPGR (sagittal), T\textsubscript{2}-weight-
ed (axial), and diffusion-weighted (axial) images prior to contrast administration and acquisition of post-contrast T\textsubscript{1}-Cube and 3D FSPGR images in the sagittal plane. Four minutes after injection of a gadolinium contrast agent (gadopentetic acid [Gd-
DTPA], 0.1 mmol/kg, Magnevist, Bayer Health-
Care, Germany) with a power injector (Meditrac\textsuperscript{®}, Indianola, PA, USA) at 2.5 mL/s followed by a 20-
\text{mL} saline flush at the same rate, T\textsubscript{1}-Cube was performed, and post-contrast 3D FSPGR images were acquired immediately following completion of T\textsubscript{1}-Cube measurements. Scan parameters for T\textsubscript{1}-Cube were: repetition time (TR)/echo time (TE), 500 ms/15.1 ms; bandwidth, 50 kHz; slice thickness, 1.2 mm; matrix, 384 × 256; flip angle, 15°; number of excitation (NEX), one; field of vision (FOV), 24 × 24 cm; acceleration factor, 2 × 2; number of slices, 160; and scan time 4 min 5 s. Scan parameters for 3D FSPGR were: TR/TE, 10.4 ms/4.4 ms; bandwidth, 31.25 kHz; slice thickness, 1.2 mm; matrix, 384 × 256; flip angle, 15°; NEX, one; FOV, 24 × 24 cm; acceleration factor, 2 × 2; number of slices, 160; and scan time, 3 min 34 s. All MR examinations were performed before conducting any antitumor therapy.

**Patients**

We considered for study 54 consecutive patients who underwent contrast-enhanced MR imaging for diagnosis of suspected brain tumors between December 10, 2012 and February 24, 2014. Two neuroradiologists (M.M., T.A.) unaware of the final diag-

gnosis of the lesion chose all enhanced lesions for image analysis. Lesions smaller than 3 mm\textsuperscript{2} were excluded. The diagnosis was made pathologically or radiologically by the consensus of 4 experienced radiologists with 10 to 16 years of experience in neuroimaging (M.T., S.I., Y.O., N.U.). Ultimately, we selected 32 patients (17 men, 15 women; mean age, 63.1 years; age range, 34 to 84 years) for study, including 9 patients with metastasis (34 le-
sions), 11 with high grade glioma (HGG, 13 lesions), 4 with primary central nervous system (CNS) lymphoma (6 lesions), and 8 with meningioma (7 meningiomas and one hemangio-
cytoma). Tu-

or specimens of 30 of the 32 patients were ob-
tained during surgery and stained with hematoxy-
lin-eosin for histopathological evaluation by an experienced neuropathologist blinded to the imag-

ing findings. Table 1 summarizes patient data.

**Data analysis**

We analyzed pre-contrast 3D FSPGR, post-
contrast 3D FSPGR, and post-contrast T\textsubscript{1}-Cube images on an Advantage workstation (AW 4.6) (GE HealthCare, Milwaukee, WI). Two neuroradiologists with 10 (M.M.) and 25 years (M.H.) of expe-

rience in neuroimaging independently measured each lesion using a region-of-interest (ROI) method. Both examiners measured the lesions twice (in the same plane and at the same anatomic level) during 2 sessions separated by at least 2 weeks. The order of cases was randomized during each session. For the first measurement of enhanced T\textsubscript{1}-Cube images, a hand-drawn polygonal ROI was defined as large as possible to include necrotic areas of the lesion. This digital ROI was then copied to the corre-

sponding post-contrast T\textsubscript{1}-Cube and pre-contrast...
3D FSPGR images. The mean signal intensity (SI) and area of the ROI were measured for each tumor. Another ROI, approximately 100 mm², was drawn on normal-appearing white matter (WM) as a reference value for calculating the contrast-to-noise ratio (CNR). Figure 1 illustrates these measurement parameters.

**Statistical analysis**

We expressed contrast enhancement using the CNR, defined as: 
\[
\text{CNR} = \frac{\text{SI}_{\text{lesion}} - \text{SI}_{\text{white matter}}}{\text{SD}_{\text{lesion}}}
\]
where \(\text{SI}_{\text{lesion}}\) represents the mean SI value of the lesion, \(\text{SI}_{\text{white matter}}\) is that of surrounding normal-appearing white matter, and \(\text{SD}_{\text{lesion}}\) is the standard deviation of the SI within the lesion. For both measurements, we used the intraclass correlation coefficient (ICC) to estimate inter-rater reliability. We used Spearman’s rank correlation to evaluate the relationship between CNR and tumor size for both post-contrast T1-Cube and post-contrast 3D FSPGR images and the Wilcoxon rank sum test to compare CNRs and subgroups between imaging modalities.

All statistical analysis was performed using Excel Statistics 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan) and Excel 2010 (Microsoft Co., Redmond, WA, USA). \(P < 0.05\) was considered significant.

**Comparison of CNR and enhancement ratio (ER) by tumor group**

We divided the contrast-enhanced lesions into 2 subgroups according to the degree of enhancement or the ER, namely, 
\[
\text{CR}_{\text{post-contrast 3D FSPGR}} / \text{CR}_{\text{pre-contrast 3D FSPGR}}
\]
and defined CR as 
\[
\text{CR} = \frac{\text{SI}_{\text{lesion}}}{\text{SI}_{\text{white matter}}}
\]

We used the median overall ER value (1.97) as the threshold for defining strong and weak enhancement subgroups. The ER of the strong enhancement group ranged from 1.98 to 2.86 (28 lesions), and the ER of the weak enhancement group ranged from 1.23 to 1.97 (33 lesions). In the strong enhancement group, histopathological type distribution was metastasis (n = 11), HGG (n = 7), meningioma (n = 7), and lymphoma (n = 3). In the weak enhancement group, histopathological type distribution was metastasis (n = 23), HGG (n = 6), meningioma (n = 1), and lymphoma (n = 3). We also analyzed the lesions according to histopathological subgroup–brain metastasis, HGG, meningioma, and lymphoma.

**Comparison of CNR by tumor size in the metastasis group**

To examine the relationship between CNR and

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>No. of Lesions</th>
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<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>F</td>
<td>Metastasis from breast cancer</td>
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</tr>
<tr>
<td>2</td>
<td>63</td>
<td>M</td>
<td>Metastasis from gastric cancer</td>
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</tr>
<tr>
<td>3</td>
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<td>M</td>
<td>Metastasis from colon cancer</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>F</td>
<td>Metastasis from colon cancer</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>M</td>
<td>Metastasis from lung cancer</td>
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</tr>
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<td>77</td>
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<td>Metastasis from lung cancer</td>
<td>6</td>
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<td>7</td>
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<td>M</td>
<td>Metastasis from lung cancer</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>F</td>
<td>Metastasis from lung cancer</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>81</td>
<td>M</td>
<td>Metastasis from RCC</td>
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<td>10</td>
<td>39</td>
<td>F</td>
<td>Meningioma</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>84</td>
<td>F</td>
<td>Meningioma</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>39</td>
<td>F</td>
<td>Meningioma</td>
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<td>70</td>
<td>F</td>
<td>Meningioma</td>
<td>1</td>
</tr>
<tr>
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<td>59</td>
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<td>1</td>
</tr>
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<tr>
<td>17</td>
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<td>F</td>
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<td>1</td>
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<td>73</td>
<td>M</td>
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</tr>
<tr>
<td>30</td>
<td>59</td>
<td>M</td>
<td>DLBCL</td>
<td>1</td>
</tr>
<tr>
<td>31</td>
<td>55</td>
<td>F</td>
<td>DLBCL</td>
<td>3</td>
</tr>
<tr>
<td>32</td>
<td>78</td>
<td>F</td>
<td>DLBCL</td>
<td>1</td>
</tr>
</tbody>
</table>

AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; DLBCL, diffuse large B-cell lymphoma; GBM, glioblastoma multiforme; RCC, renal cell carcinoma; WHO, World Health Organization.

Intracranial tumors in all except 2 patients were diagnosed by histology. The remaining 2 meningiomas in Cases 10 and 12 were diagnosed by imaging.
tumor size, we restricted analysis to the metastatic tumors because these were the most common. We measured the maximum lesion size according to the enhanced area on primary sagittal images. Very small metastatic lesions (<3 mm²) were excluded from the evaluation because of insufficient measurement reliability. We divided the metastatic lesions measured into 2 size subgroups, those larger than the median of 24.2 mm² (range, 24.9 to 1949.5 mm²) and those smaller than the median (range, 4.95 to 23.5 mm²).

Results

High inter-rater reliability was confirmed by an intra-class correlation coefficient above 0.9 for both CNR and tumor size estimates.

Comparison of tumor CNR and size as measured by T₁-Cube or 3D FSPGR

The CNR was significantly higher on T₁-Cube images than 3D FSPGR images for the entire tumor population (1.85 ± 0.97 versus 1.12 ± 1.05; Wilcoxon test, P < 0.01). Furthermore, mean tumor size was slightly larger on T₁-Cube images than on 3D FSPGR images, although the difference did not reach statistical significance (315.4 ± 497.4 mm² versus 313.1 ± 493.8 mm²; Wilcoxon test, P = 0.29).

Subgroup analyses

Metastatic tumor size

As shown in Table 2, the mean CNR was higher on T₁-Cube images than 3D FSPGR images for the large metastatic tumors, but the difference did not reach significance (1.73 ± 0.88 versus 1.21 ± 0.92, Wilcoxon test, P = 0.06). In the small metastatic tumor group, the mean CNR was significantly higher on T₁-Cube images (2.06 ± 0.83 versus 1.05 ± 0.60; Wilcoxon test, P < 0.01).

Enhancement ratio

The mean CNR was significantly higher on T₁-Cube images than 3D FSPGR images for both the strong enhancement group (1.78 ± 0.98 versus 1.25 ± 0.94; Wilcoxon test, P < 0.05) and weak enhancement group (1.90 ± 0.95 versus 1.12 ± 1.02; Wilcoxon test, P < 0.01) (Table 3).

Histopathological tumor type

As presented in Table 4, the mean CNR was also significantly higher on T₁-Cube images for the metastasis group (2.14 ± 1.04 versus 1.23 ± 0.13; Wilcoxon test, P < 0.01) and lymphoma group (1.59 ± 0.52 versus 1.08 ± 0.36; Wilcoxon test,
In the HGG group, the mean CNR was also larger on T1-Cube images, but the difference did not reach statistical significance (1.31 ± 0.58 versus 0.91 ± 0.53; Wilcoxon test, *P* = 0.12). In contrast, the mean CNR was almost the same for the meningioma group (1.68 ± 0.93 versus 1.71 ± 0.86; Wilcoxon test, *P* = 0.67).

**Discussion**

In this study, we acquired T1-Cube images before 3D FSPGR images because a longer delay after injection of contrast agent results in greater enhancement, so 3D FSPGR images would be expected to exhibit greater enhancement than T1-Cube images. However, the overall mean CNR value and most tumor subtype mean CNR values were higher on T1-Cube images. The difference in mean CNR between T1-Cube and 3D FSPGR was especially great for smaller metastatic lesions (Figs. 2, 3). To the best of our knowledge, this is the first study to demonstrate differences in contrast enhancement characteristics between T1-Cube and 3D FSPGR imaging using 3T MR imaging.

Likewise, contrast enhancement was stronger on images obtained using T1-SPACE, which also uses variable flip angle T1-weighted 3D spin-echo imaging, than on magnetization-prepared rapid gradient-echo (MPRAGE) images. Mugler and colleagues reported higher tumor detectability using 2D T1-weighted SE sequences than 3D T1-weighted GRE sequences, and Yoshida's team's reported improved detection of small brain metastases using contrast-enhanced T1-weighted volume isotropic turbo spin echo acquisition (T1-VISTA). These results are generally consistent with ours using T1-Cube 3T MR imaging.

In analyses by tumor subtype, T1-Cube images exhibited greater Gd enhancement than 3D FSPGR images for metastatic brain tumors and lymphoma, whereas mean CNR values did not differ significantly for HGG and meningiomas. The intrinsic reasons for these differences in CNR values among specific histological tumor types are not clear but may stem from differences in vascular permeability and/or extracellular space characteristics.

**Table 3.** Comparison of contrast-to-noise ratio (CNR) measured by T1-Cube and then 3-dimensional (3D) fast spoiled gradient recall acquisition in steady state (FSPGR) for strong and weak enhancement groups

<table>
<thead>
<tr>
<th></th>
<th>T1-Cube</th>
<th>3D FSPGR</th>
<th><em>P</em> value</th>
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<tbody>
<tr>
<td>Strong enhancement group</td>
<td>1.78 ± 0.98</td>
<td>1.25 ± 0.94</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Weak enhancement group</td>
<td>1.90 ± 0.95</td>
<td>1.12 ± 1.02</td>
<td>&lt;0.01</td>
</tr>
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</table>

Data are mean ± standard deviation (SD) for 28 strongly enhanced lesions and 33 weakly enhanced lesions.

**Table 4.** Comparison of contrast-to-noise ratio (CNR) measured by T1-Cube and then 3-dimensional (3D) fast spoiled gradient recall acquisition in steady state (FSPGR) for different histopathological tumor groups

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>T1-Cube</th>
<th>3D FSPGR</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>2.14 ± 1.04</td>
<td>1.23 ± 0.13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High grade glioma</td>
<td>1.31 ± 0.58</td>
<td>0.91 ± 0.53</td>
<td>0.12</td>
</tr>
<tr>
<td>Meningioma</td>
<td>1.68 ± 0.93</td>
<td>1.71 ± 0.86</td>
<td>0.67</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1.59 ± 0.52</td>
<td>1.08 ± 0.36</td>
<td>&lt;0.05</td>
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</tbody>
</table>

Data are mean ± standard deviation (SD) for 34 lesions (metastasis), 13 lesions (high grade glioma), 8 lesions (meningioma), and 6 lesions (lymphoma).
The reason for greater Gd enhancement by FSE-based T₁-Cube imaging than GRE-based 3D FSPGR imaging is also unclear, but numerous studies have reported this phenomenon. Kato and associates reported that SPACE sequences reduce the background signal via the magnetization transfer (MT) effect; specifically, a magnetization transfer prepulse suppresses the background signal for improved tumor enhancement. Similarly, the T₁-Cube sequence uses an FSE imaging technique in which multiple refocused pulses work as off-resonance pulses to provide an MT effect that reduces the background signal intensity from normal brain parenchyma. Nagao and colleagues reported that turbo spin-echo (TSE) motion-sensitized driven-equilibrium (MSDE) prepulses suppress signals from small blood vessels to further enhance detectability. In addition, detection of dural or meningeal metastases appears better by FSE images than GRE images because FSE sequences tend to reduce signals from blood vessels at the brain surface, whereas such signals are usually hyperintense on 3D GRE images. Indeed, this effect obscured smaller lesions on 3D FSPGR images in our study (Fig. 1, arrow). As an alternative, the groups of Chen and Fukuoka reported the greater sensitivity of 3D T₂ fluid-attenuated inversion recovery (T₂ FLAIR) than 3D T₁-weighted imaging for detecting contrast enhancement. However, T₂ FLAIR requires time-consuming acquisition of both pre- and post-contrast images.

Our study has several limitations. First, the number of cases was limited. Second, the scan time of T₁-Cube was about 15% longer than that of 3D FSPGR, though our study analyzed CNRs, for which scan time has relatively little influence. Several recent technical advances have contributed to a dramatic reduction in scan time, including very long echo trains through refocusing FA (flip angle) modulation and 2D accelerated parallel imaging, which may solve many problems associated with the protracted 3D FSE measurement duration. Third, other pathologies with enhancement, such as subacute infarction, may have contaminated some of the enhancing lesions.

In conclusion, we found that Gd enhancement of the same heterogeneous population of tumors was higher using T₁-Cube than 3D FSPGR, especially for smaller and weakly enhanced lesions, and suggest the superiority of T₁-Cube to 3D FSPGR for the detection of small metastatic brain lesions.

Conflict of interest: Dr. Harada received research funding from Bayer HealthCare. The other authors declare they have no conflicts of interest.

Acknowledgement

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References


Fig. 3. Appearance of small, weakly enhanced lesions on an axial T₁-Cube image (a) and the corresponding axial 3-dimensional (3D) fast spoiled gradient recall acquisition in steady state (FSPGR) image (b). Numerous weakly enhanced lesions are well delineated by T₁-Cube. These lesions were uniformly fainter on 3D FSPGR, and one small nodular lesion was barely detectable above the background on 3D FSPGR (arrow).


