Consecutive Acquisition of Time-resolved Contrast-enhanced MR Angiography and Perfusion MR Imaging with Added Dose of Gadolinium-based Contrast Agent Aids Diagnosis of Suspected Brain Metastasis

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Purpose: Time-resolved contrast-enhanced magnetic resonance (MR) angiography (TCMRA) and perfusion MR imaging (PWI) have been used to assess the hemodynamics of brain tumors. We assessed the feasibility and value of consecutive performance of these techniques to evaluate suspected brain metastasis following supplementary injection of gadolinium-based contrast medium.

Methods: In 69 patients with suspected brain metastasis, we obtained precontrast MR images followed by TCMRA and postcontrast T1-weighted images after administration of 0.1 mmol/kg gadoteridol. When findings were negative or equivocal, we injected an additional 0.1-mmol/kg dose of gadoteridol and obtained PWI and second postcontrast T1-weighted images. We used a 3-point scale to grade perfusion maps and TCMRA and assessed whether these techniques added information to conventional MR imaging in the differential diagnosis. We also evaluated whether the second contrast injection improved the conspicuity and/or number of enhancing lesions and used a 4-point scoring system to quantitatively analyze diagnostic yield of TCMRA and PWI.

Results: We could assess tumor hemodynamics on PWI maps and TCMRA images in all 69 patients. In 14 cases (20%), PWI and/or TCMRA added information to conventional MR findings. After second injection of contrast medium, lesion conspicuity improved in 58 of the 69 cases (84%), and the number of detected lesions increased in 11 of 31 cases diagnosed with metastatic disease (36%). Quantitative analysis revealed TCMRA and PWI provided significant additional diagnostic information (Kruskal-Wallis test, \( P < 0.0001 \)).

Conclusion: Consecutive acquisition of TCMRA and PWI using supplementary contrast injection can facilitate differential diagnosis of suspected brain metastasis and improve the number and conspicuity of detected lesions.

Keywords: brain metastasis, contrast agent, MRDSA, perfusion MRI, time-resolved contrast-enhanced MRA

Introduction

Perfusion magnetic resonance (MR) imaging (PWI), an established technique for semi-quantitative evaluation of brain tumor hemodynamics, provides valuable information that corresponds to histopathological changes in tumors.1-5 Accordingly, it has been used to guide tumor biopsy, plan radiosurgery, and monitor therapies. Time-resolved contrast-enhanced MR angiography (TCMRA) is used similarly to conventional digital subtraction angiography for qualitative assessment of the hemodynamics of brain tumors.6,7 We hypothe-
sized that acquisition of both PWI and TCMRA in one imaging session would increase information regarding tumor perfusion in the diagnosis of brain metastasis, which is frequently diagnosed on contrast-enhanced MR imaging. Health authorities, such as the Japanese Ministry of Health and Welfare (JMHW) and the Food and Drug Administration (FDA) of the United States, recommend using the lowest possible dose of gadolinium (Gd)-based contrast medium for diagnostic study, particularly in patients with severely impaired renal function who are at known risk for developing nephrogenic systemic fibrosis (NSF). In patients with suspected brain metastasis, we assessed the feasibility and value of performing TCMRA followed by PWI after adding a supplementary injection of Gd-based contrast medium approved by the JMHW and FDA for administration in a dose greater than 0.1 mmol/kg.

Materials and Methods

Patients

Our study participants were 69 consecutive patients (33 men, 36 women; aged 24 to 88 years; mean age, 61.2 years) scheduled for MR examination for suspected brain metastasis. Their final diagnoses, made at surgery or, in 26 patients with metastasis, clinically, included brain metastasis in 31 cases, high grade glioma in 13, low grade glioma in three, primary central nervous system lymphoma in seven, and meningioma in six as well as other diagnoses in nine, including hemangioblastoma in three, cavernous hemangioma in two, multiple sclerosis in two, radiation necrosis in one, and dysembryoplastic neuroepithelial tumor in one. Our institutional review boards approved the study protocol, and we obtained written informed consent from all patients.

MR imaging

MR examinations were performed at 3 institutions on a 1.5-tesla magnet (Excelart Vantage, Toshiba Medical Systems, Tochigi, Japan) using an identical study protocol. Imaging sequences included diffusion-weighted, fluid-attenuated inversion recovery (FLAIR), T₁-weighted spin-echo, and T₂-weighted fast spin-echo axial scans, TCMRA, and the first postcontrast T₁-weighted spin-echo scan in the axial plane. When initial findings were negative or equivocal and an attending radiologist with at least five years’ experience in neuroradiology judged further examination clinically necessary, patients were given an additional injection of contrast medium, and we performed PWI and a second postcontrast T₁-weighted spin-echo scan that included an axial scan and additional sagittal and coronal scans in most patients. Table shows details of scanning parameters of the T₁-weighted scan, TCMRA, and PWI. Using parallel imaging and efficient sampling of k-space with an acceleration factor of 3, temporal resolution of TCMRA was 0.79 s/frame. TCMRA was performed in the sagittal plane in 62 patients and the axial plane in the remaining seven.

Initial and supplementary injections of Gd-based contrast agent (gadoteridol, ProHance, Bracco, Milan, Italy) were administered at a dose of 0.2 mL/kg (0.1 mmol/kg) followed by saline flush (20 mL) using a power injector for both injections. We injected both contrast agent and saline flush at a rate of 3 mL/s. Adverse events were recorded after each contrast injection.

Image assessments

We graded tumor visualization and hemodynamics in TCMRA images and PWI maps using a 3-point scale. Grade 1 was defined as no visualization of a tumor (TCMRA) or tumor not discriminated from surrounding brain (PWI). Grade 2 indicated

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR/TE (ms)</th>
<th>Flip angle</th>
<th>Field of view (cm)</th>
<th>Matrix</th>
<th>Section thickness/interval (mm)</th>
<th>Number of sections</th>
<th>Acceleration factor</th>
<th>Scan duration (min : s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₁-weighted scan</td>
<td>Spin echo</td>
<td>496/12</td>
<td>90°</td>
<td>22×22</td>
<td>192×320</td>
<td>5/1.5</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>TCMRA</td>
<td>Fast field-echo</td>
<td>3.1/0.9</td>
<td>20°</td>
<td>26×28</td>
<td>128×256</td>
<td>7.5/NA</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>PWI</td>
<td>Field-echo echo-planar</td>
<td>2000/60</td>
<td>90°</td>
<td>25×28</td>
<td>128×128</td>
<td>5/1.5</td>
<td>15</td>
<td>2</td>
</tr>
</tbody>
</table>

NA, not applicable; PWI, perfusion magnetic resonance (MR) imaging; TCMRA, time-resolved contrast-enhanced MR angiography; TR, repetition time; TE, echo time.
visualization of tumor but poor depiction of its hemodynamics or adjacent vessels (TCMRA) or visualization of tumor and poor contrast with surrounding brain tissue (PWI). Grade 3 indicated visualization of tumor and good depiction of its hemodynamics or adjacent vessels (TCMRA) or visualization of tumor and good contrast with surrounding brain (PWI). We used the 3-point scale for separate grading of PWI maps that visualized regional cerebral blood flow, regional cerebral blood volume, and mean transit time and averaged the 3 ratings for a single value for each patient.

Next, we used another 3-point scale to grade whether TCMRA or PWI added information to conventional MR images. Grade 1 indicated that conventional MR images were sufficient for diagnosis. Grade 2 meant that TCMRA or PWI led to correct diagnosis in patients whose conventional MR images were atypical or inconclusive in terms of the differential diagnosis among neoplasms or glioma grading. Grade 3 indicated that correct diagnosis was not made even with reference to TCMRA and/or PWI. Results of these ratings were tabulated but not averaged. We assessed changes in lesion conspicuity between images obtained after first and second injections using a 4-point scale to grade degree of enhancement as: absent, Grade 1; faint, Grade 2; moderate, Grade 3; and marked, Grade 4. We also assessed the number of detected lesions after first and second injections in patients with brain metastasis.

In analyzing data of these qualitative assessments, we averaged scores in evaluating TCMRA images and PWI maps, information added by TCMRA and/or PWI, and changes in lesion conspicuity. We compared scores for TCMRA images and PWI maps using Wilcoxon’s rank test.

For quantitative assessment, we grouped MR findings from all patients into 3 groups, those of first postcontrast T1-weighted images (Group A), first postcontrast T1-weighted images and TCMRA (Group B), and first postcontrast T1-weighted images, TCMRA, and PWI (Group C)—and then categorized and rated findings in the 3 groups. Score 1 indicated that images led to incorrect diagnosis; Score 2, that images provided no valuable information in the differential diagnosis and did not lead to correct diagnosis; Score 3, that images provided valuable information in the differential diagnosis but did not lead to correct diagnosis; and Score 4, that images provided valuable information in the differential diagnosis and led to correct diagnosis. We evaluated results of the rating using Kruskal-Wallis test.

All assessments were performed independently by 2 neuroradiologists with at least 20 years’ experience in cerebral MR imaging, who resolved discrepant judgments by consensus.

Results

PWI was considered to be indicated and was performed in all of our 63 patients, and diagnostic-quality TCMRA images and PWI maps were obtained in all 63. The contrast agent was well tolerated with no adverse events recorded.

The average score in the visual assessment of TCMRA that included both tumor and adjacent vessels was 2.0, and the average score of PWI maps was 2.3 (Fig. 1), without significant difference between the 2 techniques ($P>0.05$). In 14 (20%) of the 69 cases, information added by TCMRA and/or PWI to conventional MR images led to correct diagnosis (Grade 2) (Fig. 2). In 11 of these 14 cases, differential diagnosis was precisely made after TCMRA and/or PWI, whereas in 3 cases with glioma, preoperative grading was correctly made after TCMRA and/or PWI.

Lesion conspicuity improved in 58 of the 69 cases (84%) (Fig. 3). Enhancement after second injection was Grade 3 in 13 patients and Grade 4 in 45. In 11 of the 31 patients (36%) with final diagnosis of brain metastasis, an average increase of 3.1 lesions was detected after second injection of contrast medium (Fig. 4).

In the assessment of diagnostic yield by adding TCMRA and PWI, the 3 groups (A–C) differed significantly ($P<0.0001$), indicating that addition of these 2 techniques provided significant additional diagnostic information.

Discussion

In the diagnosis of brain tumors on MR imaging, it has been widely accepted that postcontrast T1-weighted imaging adds much information to precontrast images. Both TCMRA and PWI images enable assessment of hemodynamic changes of brain tumors that are not observable on static postcontrast T1-weighted images. Dynamic susceptibility contrast PWI based on echo-planar imaging is valuable for characterizing brain tumors and related lesions based on changes in hemodynamics through capillary vessels before and after surgery. TCMRA can also be used to determine the kinetics of lesion enhancement. TCMRA is a technique advanced by the advent of parallel imaging techniques that accelerate scanning time and by 3-dimensional k-space sampling techniques that provide both good temporal resolution and acceptable
Fig. 1. A 60-year-old man with glioblastoma in the frontal lobe. (a) Postcontrast T1-weighted image after the second injection of contrast medium shows a well enhanced mass with cystic component in the frontal lobe. These findings suggest glioblastoma. (b) Selected 3 frames of time-resolved contrast-enhanced magnetic resonance (MR) angiography (TCMRA) clearly show a hypervascular mass in the frontal lobe with early filling of a large vein draining to the superior sagittal sinus (arrow). These findings also suggest glioblastoma. (c) Map of regional cerebral blood volume shows elevated blood volume in the solid part of the tumor, which is compatible with glioblastoma. In this case, both TCMRA and perfusion MR imaging (PWI) were Grade 3.

Fig. 2. A 57-year-old man with a single metastasis from rectal cancer. (a) Postcontrast T1-weighted image after the second injection of contrast medium shows a mass in the occipital lobe with ring-like enhancement and central necrosis. It is surrounded by a large area of T2 prolongation on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (not shown). These findings suggest both glioblastoma and metastasis. (b) Three frames of time-resolved contrast-enhanced magnetic resonance (MR) angiography (TCMRA) reveal that the tumor is rather hypovascular because no tumor vessel or stain is identified, which suggests that the tumor is a metastasis. (c) Map of regional cerebral blood volume shows blood volume of the solid part of the tumor comparable to that of the normal cortex, which also shows that the tumor is not hypervascular. As suggested on TCMRA and perfusion MR imaging (PWI), the final diagnosis after surgery was metastasis.
tissue contrast.

In our series, TCMRA and/or PWI directly contributed to diagnosis in 14 (20%) of the 69 cases. In patients with final diagnosis of brain metastasis, the number of lesions detected increased after the second injection in 11 of the 31 cases (36%). In two of the 11 cases, the number of lesions detected increased from one to two or three. In addition, in one patient with primary central nervous system lymphoma, lesion enhancement was visible after the second injection that was not seen after the first injection, even in retrospect. This increase in diagnostic information was obtained using a contrast dose determined by patient weight (0.2 mmol/kg cumulative dose) that is approved by the JMHW and FDA. The specific contrast agent used, gadoteridol, is well tolerated and considered to carry low risk for the development of NSF, with no unconfounded case reported to date. However, a higher risk of NSF is reported with increasing contrast dose and use of multiple injections in a short period of time. This suggests that administration of Gd-based contrast agent in patients with impaired renal function should be performed in a

Fig. 3. A 68-year-old man with multiple metastases from lung cancer. (a) Postcontrast T1-weighted image after the first injection of contrast medium shows multiple metastases. (b) Postcontrast T1-weighted image after second injection shows improved lesion conspicuity and better definition of lesion borders.

Fig. 4. A 64-year-old man with a single metastasis from lung cancer. (a) Postcontrast T1-weighted image after the first injection of contrast medium shows no abnormal enhancement. Fluid-attenuated inversion recovery (FLAIR) and T2-weighted images were unremarkable (not shown). (b) A single metastasis is visualized on postcontrast T1-weighted image after the second injection (arrow). A coronal image also demonstrated this lesion (not shown).
single session to avoid the patient’s return for another injection if TCMRA or PWI is later deemed necessary.

Consecutive acquisition of TCMRA and PWI seems feasible in clinical practice. The MR system used in this study did not require waiting for completion of image reconstruction of the last sequence, so TCMRA and PWI could be performed without interrupting subsequent scans. Data was also reconstructed in a reasonable time (PWI, < one minute; TCMRA, 10 to 15 min). For PWI, the administration of a predose of Gd-based contrast agent reportedly prevents artificially lowered estimation of regional cerebral blood volume.11,12

Our protocol may have worked well in this regard. We also utilized a short scan time for the two methods—one min 15 s for TCMRA and one min 0 s for PWI. Seminal studies of several investigators have already reported improved lesion detection and characterization on T1-weighted spin-echo images after supplementary doses of gadoteridol.13–16 Although their methods and ours differ, we all agree that the smallest possible dose of Gd-based contrast agent should be used to acquire the greatest amount of information. In our protocol, despite identical section thickness and interval, the number of sections of PWI (15 sections) was smaller than that of T1-weighted images (20 sections), which was attributed to limitations of scanner software. Although we had no patient whose PWI was affected by this issue, it may impair assessment of some lesions in patients with multiple lesions.

Our study has some limitations. First, our patient group was rather small and included only patients for whom an experienced neuroradiologist felt lesion hemodynamic information would be helpful. Second, although all patients included were referred for evaluation of suspected brain metastasis, slightly more than half of the patients had other lesion types as the final diagnosis. However, in practice, contrast-enhanced MR imaging is often used to provide a more definitive diagnosis in patients with suspected metastatic disease, so the variety of lesions observed in our patients reflects actual clinical practice. Although our protocol is intended for evaluation of brain metastasis, it may be effective in distinguishing tumor recurrence from necrosis, which we experienced in a single case, after stereotactic radiosurgery or other similar therapeutic methods.

Our method may warrant further investigation in a larger series that investigates not only preoperative differential diagnosis but also effect on patient management. Furthermore, assessment of Gd-based contrast agents with higher relaxivity as well as imaging at 3T could be warranted as possible ways to reduce the total amount of contrast agent injected, particularly in patients at risk for developing NSF.17–20

In conclusion, consecutive acquisition of TCMRA and PWI using a supplementary injection of a Gd-based contrast agent can facilitate preoperative differential diagnosis in patients with suspected brain metastasis. This method also increases the number and conspicuity of lesions detected in patients with suspected metastatic disease to the brain.

References


16. Brekenfeld C, Foert E, Hundt W, Kenn W, Lodeann KP, Gehl HB. Enhancement of cerebral diseases: how much contrast agent is enough? Comparison of 0.1, 0.2, and 0.3 mmol/kg gadoteridol at 0.2T with 0.1 mmol/kg gadoteridol at 1.5T. Invest Radiol 2001; 36:266–275.


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