Detection of small brain metastases using 3T MR imaging: comparison of diagnostic performance among contrast-enhanced T1-weighted SPACE, MPRAGE, SE, IR, and 2D FLASH imaging

Poster No.: C-0282
Congress: ECR 2015
Type: Scientific Exhibit
Keywords: Neuroradiology brain, Head and neck, Oncology, MR, Comparative studies, Cancer
DOI: 10.1594/ecr2015/C-0282

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Aims and objectives

Introduction

Brain metastases occurs in 20-40% of patients with systemic cancer [1]. The incidence and prevalence of brain metastases are increasing due to early detection with advanced imaging techniques. The therapeutic managements for brain metastases are usually based on a diagnosis using contrast-enhanced MR imaging.

The patient outcome depends on the number, size, and location of metastatic brain lesions. Identification of the number, size, and location of metastatic lesions is particularly necessary for stereotactic radiosurgery (SRS) [2]. For patients with #4 metastatic lesions or small lesions measuring less than 10 mm in diameter, aggressive treatment such as stereotactic radiosurgery (SRS) or surgical resection (SR) is recommended [3, 4]. Thus, early accurate diagnosis of metastatic brain lesions by using MR images is crucial for optimal treatment.

Contrast-enhanced T1-weighted MR imaging has become commonly used for detecting metastatic brain lesions. 2D contrast-enhanced spin-echo (SE) sequence is conventionally used at 1.5T MR imaging. However, at 3T MR imaging, motion artifacts (flow-related artifacts) tend to be worse than 1.5T in 2D SE sequence [2]. Also, if slice thinner than 3 mm it leads to decreased signal-to-noise ratio (SNR) and low contrast between gray and white matter on SE image [5, 6]. Several studies have suggested that inversion recovery (IR) sequence provide higher contrast-noise-ratio (CNR) than SE sequence [7, 8]. However, Qian et al. showed that since SE sequence is more sensitive than IR sequence, IR could not replace SE sequence [9]. Moreover, the inherent blurring of the IR sequence can lead to poor performance for very small lesions [8].

Generally, Magnetization-prepared rapid gradient echo (MPRAGE), a 3D contrast-enhanced GE sequence provides higher detectability of small brain metastases than 2D SE sequence at 3T [10, 11]. MPRAGE can provide higher spatial resolution, it is possible to not only determine the extent of the lesion more precisely but also find additional lesions [6, 12]. However, on MPRAGE, normal blood vessels on the brain surface or in the sulci were frequently mistaken as metastatic lesions [5, 10].

Recently, T1-weighted sampling perfection with application-optimized contrasts by using different flip angle evolutions (SPACE), a 3D fast SE sequence was introduced to selective blood vessel suppression [5, 13].
Several previous studies show that SPACE sequence improves detection of metastatic lesions relative to MPRAGE sequence [5, 10, 14]. However, no study has been conducted comparison more than five T1-weighted contrast-enhanced sequences for detection of identical metastatic lesion.

Thus, the aim of this study was to compare the diagnostic performance of five T1-weighted sequences including SPACE, MPRAGE, conventional 2D SE, IR, and 2D FLASH after intravenous administration of contrast medium for the detection of small brain metastases at 3T.
Methods and materials

Patient selection

Between October 2011 and May 2012, 258 consecutive patients who underwent 3T MR imaging for the evaluation of brain metastases were retrospectively reviewed. We identified those who had metastatic lesions by reviewing initial contrast-enhanced MR imaging of each patient. All these images were evaluated by two experienced neuroradiologists.

For the current study, we selected all patients who fulfilled the following inclusion criteria:

(a) Tumor only located in the brain parenchyma, (b) It underwent follow-up MR imaging more than 1 month after the initial study, (c) It increased or decreased in size or decreased on follow-up MR imaging after radiation therapy with or without chemotherapy.

Among these 258 patients, 55 patients were initially selected as brain metastases. One patient with large metastatic lesion (≥10 mm in diameter) was excluded because our purpose was to evaluate the detectability of small metastases less than 10 mm in diameter.

We also excluded 17 patients who had more than 10 metastatic lesions because we considered it difficult to identify individual lesions.

Finally, 37 patients with 121 lesions (21 men, 16 women; mean age, 62.4 years; range, 36-88 years) were included in this study.

The distributions of primary malignancies of the patients were as follows: lung cancer (n = 32), gastric cancer (n = 1), breast cancer with colon cancer (n = 1), ovarian cancer (n = 1), lung cancer with hepatocellular carcinoma (n = 1), and malignant peripheral nerve sheath tumor (n = 1).

MR Imaging

All examinations were performed with a 3T MR imaging system (Magnetom Verio; Siemens, Erlangen, Germany) by using a 12-channel head coil. Before obtaining contrast-enhanced T1-weighted images, we obtained the routine precontrast imaging including 2D T1-weighted (FLASH, axial and sagittal), T2-weighted (fast SE, axial).
Contrast-enhanced 3D imaging was performed after injection of the standard dose (0.2 mmol/kg) of Gadobutrol (Gadovist®; Bayer Schering Pharma, Berlin, Germany) by using the following parameters:

The parameters for SPACE imaging were: repetition time (TR), 750 milliseconds (ms); echo time (TE), 10 ms; iPAT, 2; Turbo factor, 52; echo spacing, 3.36 ms; field of view (FOV), 256 × 256mm; matrix, 256 × 256; bandwidth, 781 Hz/pixel; slice thickness, 1 mm; number of slices, 176; scan time, 4 minutes 50 seconds,

The parameters for MPRAGE imaging were: TR, 1900 ms; TE, 2.3 ms; inversion time (TI), 900 ms; flip angle, 9 degrees; iPAT, 2; echo spacing, 6.9 ms; FOV, 256 × 256 mm; matrix, 350 × 263; bandwidth, 190 Hz/pixel; slice thickness, 1 mm; number of slices, 176; scan time, 4 minutes 26 seconds,

The parameters for 2D SE imaging were: TR, 700 ms; TE, 8.9 ms; FOV, 198 × 220 mm; matrix, 320 × 216; bandwidth, 170 Hz/pixel; slice thickness, 5 mm; number of slices, 25; scan time, 2 minutes 33 seconds

The parameters for IR imaging were: TR, 2000 ms; TE, 13 ms; FOV, 198 × 220 mm; matrix, 320 × 216; bandwidth, 200 Hz/pixel; flip angle, 150 degrees; slice thickness, 5 mm; number of slices, 25; scan time, 3 minutes 40 seconds,

The parameters for 2D FLASH imaging were: TR, 191 ms; TE, 2.85 ms; TI, 858.5 ms; FOV, 199 × 220 mm; matrix, 320 × 218; bandwidth, 340 Hz/pixel; flip angle, 70 degrees; slice thickness, 5 mm; number of slices, 25; scan time, 2 minutes 5 seconds.

To avoid timing bias after contrast injection, we alternated the order of the five sequences every two week. To reduce scan time, we acquired sagittal planes covering the whole brain for SPACE and MPRAGE, and then images were reformatted in transverse plane.

Image Analysis

Three of board-certified radiologists (G.H.C, E.J.C, J.S.S) participated in the observer test. Aside from knowing that all patients were at risk for brain metastases, all observers were blinded to other clinical information. They separately reviewed the post-contrast images of five sequences (SPACE, MPRAGE, 2D SE, IR, and 2D FLASH), in random order. Only the axial postcontrast images were available for assessment on a PACS workstation (Maroview; Infinitt, Seoul, Korea).
To minimize recall bias, each observer took part in five reading sessions with at least 3-4 weeks interval. We randomly chose 37 patients out of 203 patients from 258 patients who did not have metastatic lesion. In each reading session, the 74 cases (37 patients of metastatic group, 37 patients of nonmetastatic group were presented in a randomized order.

They recorded the location of metastatic lesions, placing an electronic annotation in each location. One of 4-point confidence scale was assigned: 1, probably not present; 2, possibly present; 3, probably present; 4, definitely present.

**Statistical Analysis**

The observers’ diagnostic performance in detecting brain metastases for each imaging modality was evaluated by using a jackknife alternative free-response receiver operating characteristic (JAFROC) analysis [15]. Calculations were performed with JAFROC analysis software (JAFROC v. 1.0, D.P. Chakraborty). The software computes a figure of merit (FOM), which is defined as the probability that a metastatic lesion is rated higher than the highest-rated not metastatic lesion on normal images.

We also evaluated the sensitivities and positive predictive values of each MR imaging sequence by dividing into two lesion size groups: # 5 mm and < 5 mm. The sensitivity of each observer with each MR imaging sequence was assessed by regarding the number of lesions assigned a confidence scale of both 3 and 4 (probably present and definitely present) as positive findings.

The McNemar test was used to compare the statistical significance of any difference in sensitivities among all MRI sequences for each observer.

For all tests, P-values less than 0.05 were considered statistically significant.

Kappa(#) statistic was used to assess interobserver agreement for the detection of metastatic lesions with each MR imaging sequence. The strength of agreement can be interpreted as follows: (# = 0.00-0.20, poor agreement; # = 0.21-0.40, fair agreement; # = 0.41-0.60, moderate agreement; # = 0.61-0.80, good agreement; # = 0.81-1.00, excellent agreement) [16].

Statistical analyses were performed using the Medcalc version 12.0 for windows.
Results

The figure of merit (FOM) as an index of diagnostic performance derived by the JAFROC analysis with 5 MRI sequences was shown in Table 1.

The average value of FOM with SPACE (mean, FOM = 0.94) was significantly highest, and followed by MPRAGE (mean, FOM = 0.83), SE (mean, FOM = 0.81), IR (mean, FOM = 0.80), and 2D FLASH (mean, FOM = 0.74) (all $P < 0.05$) (Fig. 1).

Fig 2 shows the superiority of SPACE image. SPACE image shows clearly enhancing metastatic nodular lesion than any other images.

The sensitivities and positive predictive values with 5 MRI sequence and for each observer are summarized in Table 2. For all observers, the sensitivities of SPACE image were significantly higher than those of any other sequences ($P < 0.05$). No significant difference in positive predictive value was observed among the 5 MRI sequences.

There were a total of 38 false-positive findings for all sequences (Table 3). The causes for the false-positive findings were vessels (25 lesions, 65.8%), flow artifacts (11 lesions, 29%), choroid plexus (one lesion, 2.6%), and partial volume artifact (one lesion, 2.6%). Vessels were the most commonly mistaken as metastases, followed by flow artifacts. Flow artifacts were more prominent on SE, IR, 2D FLASH sequences than on SPACE and MPRAGE sequences, whereas vessels were the most frequent cause of false-positive events on SPACE than other sequences.

The interobserver agreement for interpretation of all sequences was good (median # value, 0.72; 0.72 for SPACE, 0.76 for MPRAGE, 0.71 for SE, 0.73 for IR, and 0.70 for the 2D FLASH).
Table 1: Results of Alternative Free-Response ROC Analysis for the detection of brain metastases

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<table>
<thead>
<tr>
<th>MRI sequence</th>
<th>FOM value</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observer 1</td>
<td>Observer 2</td>
<td>Observer 3</td>
<td>Mean</td>
</tr>
<tr>
<td>SPACE</td>
<td>0.95 (0.90-0.98)</td>
<td>0.92 (0.92-0.96)</td>
<td>0.96 (0.90-0.99)</td>
<td>0.94</td>
</tr>
<tr>
<td>MPRAGE</td>
<td>0.81 (0.77-0.90)</td>
<td>0.83 (0.78-0.89)</td>
<td>0.87 (0.76-0.91)</td>
<td>0.83</td>
</tr>
<tr>
<td>SE</td>
<td>0.80 (0.75-0.87)</td>
<td>0.81 (0.75-0.87)</td>
<td>0.82 (0.79-0.83)</td>
<td>0.81</td>
</tr>
<tr>
<td>IR</td>
<td>0.81 (0.74-0.86)</td>
<td>0.77 (0.75-0.85)</td>
<td>0.81 (0.74-0.86)</td>
<td>0.80</td>
</tr>
<tr>
<td>2D FLASH</td>
<td>0.73 (0.68-0.81)</td>
<td>0.76 (0.68-0.81)</td>
<td>0.74 (0.70-0.79)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Data in parenthesis are 95% CI.

Table 2: Comparison of the sensitivities of the sequences by dividing into two lesion size groups

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<table>
<thead>
<tr>
<th>Observer</th>
<th>Diameter(mm)</th>
<th>SPACE</th>
<th>MPRAGE</th>
<th>SE</th>
<th>IR</th>
<th>2D FLASH</th>
<th>$P$ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 5 mm</td>
<td>92.5</td>
<td>87.5</td>
<td>85.0</td>
<td>87.5</td>
<td>77.5</td>
<td>0.625</td>
</tr>
<tr>
<td></td>
<td>&lt; 5 mm</td>
<td>84.0</td>
<td>48.1</td>
<td>42.0</td>
<td>35.8</td>
<td>25.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2</td>
<td>≥ 5 mm</td>
<td>95</td>
<td>87.5</td>
<td>95</td>
<td>87.5</td>
<td>87.5</td>
<td>0.453</td>
</tr>
<tr>
<td></td>
<td>&lt; 5 mm</td>
<td>81.5</td>
<td>53.1</td>
<td>51.9</td>
<td>38.3</td>
<td>42.0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>3</td>
<td>≥ 5 mm</td>
<td>95</td>
<td>92.5</td>
<td>92.5</td>
<td>87.5</td>
<td>77.5</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>&lt; 5 mm</td>
<td>90.1</td>
<td>64.2</td>
<td>53.1</td>
<td>58.0</td>
<td>37.0</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

* $P$ values for comparisons among five sequences of each observer.
Table 3: False-Positive Findings for Five Sequences

<table>
<thead>
<tr>
<th>False-Positive Findings</th>
<th>SPACE</th>
<th>MPRAGE</th>
<th>SE</th>
<th>IR</th>
<th>2D FLASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessels</td>
<td>15</td>
<td>3</td>
<td>-</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Choroid plexus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Flow artifact</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Partial volume artifact</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

Numbers are those of false positive findings that observed in each sequences

Table 3: False-Positive Findings for Five Sequences

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Fig 1. JAFROC curves for five MR pulse sequences images. Observer performance is quantified as the area under the JAFROC curve. SPACE image shows the highest diagnostic performance. The y-axis shows the lesion localization fraction and the x-axis shows false-positive fraction of images.

Fig. 1: JAFROC curves for five MR pulse sequences images. Observer performance is quantified as the area under the JAFROC curve. SPACE image shows the highest
diagnostic performance. The y-axis shows the lesion localization fraction and the x-axis shows false-positive fraction of images.

Fig. 2: The five axial contrast-enhanced images acquired with SPACE (A), MPRAGE (B), SE (C), IR (D), and 2D FLASH (E). The SPACE image (A) clearly reveals an enhancing nodular lesion in the left inferior frontal gyrus (arrow), whereas the MPRAGE image shows a faint enhancement (arrow) (B). The lesion is hardly visible on the other images (C, D, E). This may explain the superior lesion detection was performed with the SPACE image than other images.
Conclusion

3D T1-weighted SPACE sequence showed significantly higher diagnostic performance and sensitivity in detection of small brain metastases as compared to MPRAGE, SE, IR, and 2D FLASH.

Our results suggest that postcontrast T1-weighted SPACE sequence should be obtained for the detection of small brain metastases at 3T.

Limitations

There were some limitations in our study.

First, there were no pathologic confirm diagnosis of the metastatic lesions because most of patients with multiple brain metastases generally do not receive surgical treatment. In this study, we carefully selected patients who underwent follow-up MR imaging studies after the initial study and as we mentioned above, we set criteria and went through each to determine metastatic lesion. Therefore, we believe that we minimized false-positive event.

Second, the observers were not perfectly blinded about the pulse sequences because it is easy to distinguish between SPACE and MPRAGE sequences. These two sequences differ from each other regarding the gray-white matter distinction. This point could introduce bias.

Finally, the difference of image acquisition time of the five post-contrast images may affect the detection of brain metastases. To avoid this timing bias after contrast injection, we alternated the order of the five sequences by rotation.
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