Technetium-99m Sestamibi Single Photon Emission Computed Tomography Findings Correlated With P-glycoprotein Expression, Encoded by the Multidrug Resistance Gene-1 Messenger Ribonucleic Acid, in Intracranial Meningiomas

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Abstract

The present study evaluated whether technetium-99m sestamibi (99mTc-MIBI) single photon emission computed tomography (SPECT) characteristics of intracranial meningioma are correlated with the histological malignancy, proliferative potential, and P-glycoprotein (Pgp) expression, encoded by the multidrug resistance gene-1 (MDR-1) messenger ribonucleic acid (mRNA). Twenty-one patients with intracranial meningiomas, including 17 benign and four nonbenign meningiomas, underwent 99mTc-MIBI SPECT imaging at 15 minutes (early) and 3 hours (delayed) after injection. The tumor-to-normal pituitary gland ratio was calculated on both early (ER) and delayed (DR) images. Retention index (RI) was calculated using the following formula: (DR - ER)/ER × 100%. Meningioma specimens were examined by immunohistochemistry using anti-Pgp and MIB-1 monoclonal antibody. MDR-1 mRNA expression was also investigated using reverse transcription-polymerase chain reaction assay. 99mTc-MIBI was highly accumulated and retained in the tumors. 99mTc-MIBI SPECT findings were not related to MIB-1 labeling index. 99mTc-MIBI SPECT RI of the Pgp-positive group (−9.12 ± 22.27%) was significantly lower than that of the Pgp-negative group (28.79 ± 22.80%) (p = 0.0016). No significant difference was seen in ER and DR between the positive and negative groups. These results show that 99mTc-MIBI may not be useful for determining proliferative potential and histological malignancy, but could predict anticancer drug resistance related to the expression of MDR-1 mRNA and its gene product Pgp in patients with intracranial meningiomas.

Key words: meningioma, technetium-99m sestamibi, single photon emission computed tomography, multidrug resistance gene, P-glycoprotein

Introduction

Thallium-201 chloride (201Tl Cl) single photon emission computed tomography (SPECT) is useful for identifying a variety of tumors, including brain tumors. 201Tl Cl uptake is correlated with malignancy or proliferative potential in brain tumors. The retention of 201Tl as measured by 201Tl Cl SPECT is predictive of the malignant potential in meningiomas. Technetium-99m sestamibi (99mTc-MIBI), a lipophilic radiopharmaceutical, was developed as an alternative to 201Tl for myocardial perfusion imaging, and is known to be taken up by various types of tumors including brain tumors. 99mTc-MIBI SPECT is clinically useful for distinguishing between high-grade and low-grade gliomas. The uptake of 99mTc-MIBI depends on the distribution of regional blood flow and on mitochondrial oxidation capacity, which is an indicator of cell viability. 99mTc-MIBI is also a substrate for P-glycoprotein (Pgp)-mediated transport. The accumulation rates are driven by negative transmembrane potentials, but retention of 99mTc-MIBI is reduced in cells with a multidrug-resistant phenotype because of increased expression of the energy-
dependent Pgp efflux pump, which expels the substrates from the cell. Previous studies have shown an inverse relationship between the levels of Pgp and the balance of \(^{99m}\text{Tc-MIBI}\) uptake and washout rates in tumor cells. However, little is known about such features of \(^{99m}\text{Tc-MIBI}\) SPECT in intracranial meningiomas.

The present study evaluated whether \(^{99m}\text{Tc-MIBI}\) SPECT shows correlations with histological malignancy, proliferative potential, or Pgp expression, as encoded by the multidrug resistance gene-1 (MDR-1) messenger ribonucleic acid (mRNA), in intracranial meningiomas.

**Materials and Methods**

I. Tumor samples

Twenty-one patients, 18 females and three males aged 32 to 74 years (mean 56.4 years), underwent surgery for meningiomas in the Department of Neurological Surgery of Kagawa Medical University Hospital between April 1997 and November 1999. The objects and methodology of the study were explained to all patients and their families. The tumors were classified by histological subtype according to World Health Organization criteria into nine fibroblastic, six meningothelial, two transitional, three atypical, and one anaplastic. The cases of benign group, the other subtypes formed the atypical and anaplastic meningiomas formed the nonbenign group, and the other subtypes formed the benign group.

Tumor volume was obtained by drawing regions of interest around the areas of enhanced tumor mass on \(T_1\)-weighted magnetic resonance (MR) images with gadolinium, and the area of the region of interest was multiplied by the slice thickness plus the interslice gap to estimate the volume of tumor for each slice. These volumes were then summed to give the total volume of the tumor.

II. \(^{99m}\text{Tc-MIBI}\) SPECT imaging

\(^{99m}\text{Tc-MIBI}\) SPECT imaging was performed with a fan-beam collimator and a triple-head gamma camera (Picker Prism 3000; Picker International, Cleveland, Ohio, U.S.A.), which was interfaced with a dedicated computer (ODYSSSEY; Picker International). Early SPECT imaging was performed 15 minutes after the intravenous injection of 600 MBq \(^{99m}\text{Tc-MIBI}\), and delayed SPECT imaging was performed 3 hours after the injection. SPECT images of the head used 72 projections obtained using a \(64 \times 64\) matrix for a 60-second view in a step-and-shoot mode. The system was 7.2 mm full width at half maximum, and the slice thickness was 6.88 mm. The SPECT images were compared with brain MR images. The accumulation in meningiomas was evaluated by the same radiologist in all cases. Semiquantitative analysis of abnormal uptake of \(^{99m}\text{Tc-MIBI}\) was performed by drawing identical regions of interest over the tumor uptake area and the normal pituitary gland area on the transverse section that demonstrated the lesion most clearly. The mean region of interest values (total counts/total pixels) were measured, and the tumor-to-normal pituitary gland (T/N) ratios were obtained. The T/N ratio of the early images was called the early ratio (ER), and the T/N ratio of delayed image was called the delayed ratio (DR). Semiquantitative evaluation of the retention in the lesion used a retention index (RI) calculated as: \((\text{DR} - \text{ER})/\text{ER} \times 100\%\).

III. Immunohistochemistry

Pgp expression was evaluated immunohistochemically on formalin-fixed, paraffin-embedded sections using monoclonal antibody against Pgp (JSB-1; Progen Biotechnik, Heidelberg, Germany). Proliferative potentials were examined using MIB-1 monoclonal antibody (Immunotech, Marseille, France) against Ki-67 antigen by the streptavidin-biotin method.

Tissue sections (6 \(\mu\)m thick) were deparaffinized in xylene, rehydrated through a graded alcohol series, and immersed for 15 minutes in phosphate-buffered saline. For antigen retrieval, the sections were microwaved in a 0.01 M citrate buffer (pH 6.0) for 20 minutes. After microwave pretreatment, the endogenous peroxidase activity was blocked by immersion in a 3% hydrogen peroxidase/methanol solution for 10 minutes, and nonspecific staining was then blocked by 20-minute incubation with normal horse serum. The sections were then incubated overnight at 4°C with the primary antibodies (JSB-1, 1:50 dilution; MIB-1, 1:50 dilution) in a humidity chamber. The sections were treated for 30 minutes with biotinylated horse secondary antibody against mouse immunoglobulin (ABC Elite; Vector Lab., Burlingame, Calif., U.S.A.) and for 30 minutes with avidin-biotin complex (ABC Elite), followed by 0.06% dianinobenzidine with 0.01% hydrogen peroxidase for 5 minutes. The slides were lightly counterstained with hematoxylin. Control staining was obtained by omitting the primary antibody. The tumors were classified into three groups according to the distribution of Pgp expression and the intensity of immunostaining as follows: ++, weak staining or less than 10% of the specimens; +++, diffuse positive and dense or moderate staining; and −, completely absent staining.

The MIB-1 labeling index (LI) was calculated as the percentage of tumor cells that were MIB-1.
positive. More than 1000 tumor cells in randomly chosen microscopic fields were examined, and the percentage of MIB-1-positive cells was calculated.

**IV. Reverse transcription-polymerase chain reaction (RT-PCR)**

Total RNA was isolated from frozen tissue samples using ISOGEN reagent (Nippon Gene, Toyama). In brief, 100 mg of each tissue was homogenized in 1 ml of ISOGEN. Subsequently, 0.2 ml of chloroform was added and the mix was centrifuged to separate the solution into an aqueous phase containing RNA, an interphase containing deoxyribonucleic acid (DNA), and an organic phase containing protein. The aqueous layer was aspirated and added to 0.5 ml of isopropanol for RNA precipitation. Following this, the solution was centrifuged, then the pellet was washed with 75% ethanol and centrifuged again. The RNA was collected into 50 μl of diethylpyrocarbonate-treated water. RT-PCR was performed using a First-Strand Complementary DNA Synthesis Kit (Amersham Pharmacia Biotech, Woerden, The Netherlands). Total RNA (1 μg) was added to 14 l of RT mixture. After mixing, the samples were incubated at 37°C for 45 minutes, 95°C for 5 minutes, and 4°C for at least 5 minutes. Two oligodeoxynucleotide primers were synthesized with the sequences 5'-GCCTGGCAGCTGGAAGACAAATACACAAATT-3' and 5'-CAGACAGCAGCTGACAGTCAAACACAGGACT-3' for MDR-1, and 5'-ATCACCATTGGAATGAGCG-3' and 5'-TTGAAGGTAAACGTGAT-3' for β-actin. PCR mixture (35 μl) containing 10 nM primers and Taq DNA polymerase (Amersham Pharmacia Biotech) was added to the RT products. Initial denaturation for 2 minutes at 94°C was followed by 30 cycles of 1 minute at 94°C, 1 minute at 55°C, 2 minutes at 72°C, and final extension for 6 minutes at 72°C. The PCR products were separated on 2% agarose gels, and ethidium bromide-stained bands were recorded by Mupid-2R (Cosmo-Bio, Tokyo). The expressed sizes of the PCR products were 283 bp for MDR-1 and 93 bp for β-actin. The PCR product of MDR-1 was semiquantitatively analyzed with NIH Image Version 1.61. The MDR-1 mRNA:β-actin signal was calculated for each specimen.

### Table 1: Clinical, single photon emission computed tomography (SPECT), immunohistochemical, and molecular biological characteristics of 21 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Histology</th>
<th>Volume (cm³)</th>
<th>99mTc-MIBI SPECT</th>
<th>P-glycoprotein staining pattern*</th>
<th>MDR-1: β actin</th>
<th>MIB-1 LI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ER DR RI (%)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>70</td>
<td>F</td>
<td>Fib</td>
<td>33.5</td>
<td>1.51 1.78 17.9</td>
<td>–</td>
<td>0.78</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>F</td>
<td>Fib</td>
<td>4.6</td>
<td>1.14 1.25 9.6</td>
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<td>ND</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>F</td>
<td>Fib</td>
<td>68.0</td>
<td>1.98 2.31 16.7</td>
<td>–</td>
<td>ND</td>
<td>5.3</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>F</td>
<td>Fib</td>
<td>9.8</td>
<td>1.50 2.61 74.0</td>
<td>–</td>
<td>0.32</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>M</td>
<td>Fib</td>
<td>18.8</td>
<td>1.45 1.18 –18.6</td>
<td>+</td>
<td>ND</td>
<td>0.1</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>F</td>
<td>Fib</td>
<td>25.6</td>
<td>1.58 1.34 –15.2</td>
<td>+</td>
<td>0.78</td>
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<tr>
<td>7</td>
<td>53</td>
<td>F</td>
<td>Fib</td>
<td>42.4</td>
<td>0.97 0.67 –28.9</td>
<td>+</td>
<td>ND</td>
<td>0.1</td>
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<tr>
<td>8</td>
<td>57</td>
<td>F</td>
<td>Fib</td>
<td>62.8</td>
<td>3.40 3.43 0.9</td>
<td>+</td>
<td>ND</td>
<td>0.3</td>
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<tr>
<td>9</td>
<td>65</td>
<td>F</td>
<td>Fib</td>
<td>13.7</td>
<td>1.21 1.43 18.2</td>
<td>+</td>
<td>1.04</td>
<td>0.5</td>
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<tr>
<td>10</td>
<td>62</td>
<td>F</td>
<td>Men</td>
<td>11.4</td>
<td>1.72 2.44 41.9</td>
<td>–</td>
<td>0.21</td>
<td>1.3</td>
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<tr>
<td>11</td>
<td>48</td>
<td>F</td>
<td>Men</td>
<td>4.1</td>
<td>1.27 0.53 –58.3</td>
<td>+</td>
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<td>0.1</td>
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<tr>
<td>12</td>
<td>60</td>
<td>F</td>
<td>Men</td>
<td>33.5</td>
<td>1.72 1.25 –27.3</td>
<td>+</td>
<td>ND</td>
<td>0.1</td>
</tr>
<tr>
<td>13</td>
<td>65</td>
<td>F</td>
<td>Men</td>
<td>31.4</td>
<td>3.99 4.09 2.5</td>
<td>+</td>
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<td>0.9</td>
</tr>
<tr>
<td>14</td>
<td>32</td>
<td>F</td>
<td>Men</td>
<td>29.3</td>
<td>1.13 1.21 7.1</td>
<td>+</td>
<td>1.19</td>
<td>3.1</td>
</tr>
<tr>
<td>15</td>
<td>50</td>
<td>F</td>
<td>Men</td>
<td>25.1</td>
<td>1.72 1.61 –6.4</td>
<td>+</td>
<td>ND</td>
<td>2.7</td>
</tr>
<tr>
<td>16</td>
<td>63</td>
<td>M</td>
<td>Tran</td>
<td>25.1</td>
<td>2.16 1.43 –33.8</td>
<td>+</td>
<td>1.18</td>
<td>3.0</td>
</tr>
<tr>
<td>17</td>
<td>58</td>
<td>F</td>
<td>Tran</td>
<td>33.5</td>
<td>2.07 2.25 8.7</td>
<td>+</td>
<td>1.24</td>
<td>0.8</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
<td>F</td>
<td>Aty</td>
<td>79.2</td>
<td>1.55 2.02 30.3</td>
<td>–</td>
<td>ND</td>
<td>4.2</td>
</tr>
<tr>
<td>19</td>
<td>45</td>
<td>F</td>
<td>Aty</td>
<td>38.0</td>
<td>2.26 2.34 3.5</td>
<td>+</td>
<td>0.56</td>
<td>10.4</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
<td>M</td>
<td>Aty</td>
<td>47.1</td>
<td>1.76 2.11 19.9</td>
<td>+</td>
<td>0.42</td>
<td>1.0</td>
</tr>
<tr>
<td>21</td>
<td>59</td>
<td>F</td>
<td>Ana</td>
<td>115.4</td>
<td>1.53 1.72 12.4</td>
<td>–</td>
<td>0.28</td>
<td>3.8</td>
</tr>
</tbody>
</table>


*Neurol Med Chir (Tokyo) 43, December, 2003*
V. Statistical analysis

Correlations were evaluated using the Pearson correlation coefficient (r). The values of each T/N ratio and RI were expressed as mean ± standard error. To test for differences between these parameters, Student’s t-test was used. Correlations were analyzed using the Pearson product moment test and linear regression. Results were considered significant at p < 0.05.

Results

The age and sex of the patients, the histological type, and the tumor volume are summarized in Table 1, together with the results of 99mTc-MIBI (Fig. 1), Pgp and MDR-1 mRNA expression, and MIB-1 LI. There were no statistical correlations between age, sex, or tumor volume and ER, DR, or RI of 99mTc-MIBI SPECT.

Table 2 Single photon emission computed tomography (SPECT) characteristics and MIB-1 labeling index (LI) in various types of meningioma

<table>
<thead>
<tr>
<th>Histology</th>
<th>MIB-1 LI (%)</th>
<th>99mTc-MIBI SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ER</td>
</tr>
<tr>
<td>Benign meningioma (n = 17)</td>
<td>1.29 ± 1.50*</td>
<td>1.80 ± 0.80</td>
</tr>
<tr>
<td>Fibrous type (n = 9)</td>
<td>1.10 ± 1.73**</td>
<td>1.64 ± 0.72</td>
</tr>
<tr>
<td>Meningothelial type (n = 6)</td>
<td>1.37 ± 1.28</td>
<td>1.93 ± 1.04</td>
</tr>
<tr>
<td>Transitional type (n = 2)</td>
<td>1.90 ± 1.56</td>
<td>2.12 ± 0.06</td>
</tr>
<tr>
<td>Nonbenign meningioma (n = 4)</td>
<td>4.85 ± 3.96***</td>
<td>1.78 ± 0.34</td>
</tr>
</tbody>
</table>

Values are mean ± standard error. *p = 0.0063, **p = 0.0321. DR: delayed uptake ratio, ER: early uptake ratio, RI: retention index, 99mTc-MIBI: technetium-99m sestamibi.

I. Relationships between 99mTc-MIBI SPECT and histology or proliferative potential

The ER, DR, and RI of 99mTc-MIBI SPECT were not related to the histological type, and there were no statistical differences between the histological types (Table 2). The MIB-1 LIs of histologically benign meningiomas ranged from 0.1% to 5.3%, whereas those of nonbenign meningiomas ranged from 1.0% to 10.4%. The mean MIB-1 LI of the benign meningiomas (1.29 ± 1.50%) was significantly lower than that of the nonbenign meningiomas (4.85 ± 3.96%) (p = 0.0063, Table 2). There was no correlation between the MIB-1 LI and ER, DR, or RI of 99mTc-MIBI SPECT (Table 2).

II. Immunohistochemical results

The results of Pgp immunohistochemistry are summarized in Table 1. Positive reactions for Pgp were detected, mainly in the cytoplasm of the tumor

Fig. 1 Neuroimaging findings in a 65-year-old female with meningioma. T1-weighted magnetic resonance image with contrast medium (A) showing a homogeneously enhanced mass in the left parietal lobe. Early (B) and delayed (C) technetium-99m sestamibi single photon emission computed tomography images revealing intense radiotracer accumulation in the region of the lesion mass.

Fig. 2 Photomicrograph showing positive reactivity for P-glycoprotein, mainly in the cytoplasm of meningioma cells, and very rarely in the tumor vessels. ×400.
cells, in 14 of 21 (66.7%) meningiomas, whereas positive reactions were very rare in the tumor vessels (Fig. 2). In this study, the specimens with weak staining less than 10% of the specimens (+), or diffuse with dense or moderate staining expression (+ +) were evaluated as one group as Pgp-positive expression, whereas the other specimens with no expression were included as the Pgp-negative group, to achieve statistical significance.

III. RT-PCR results

RT-PCR was performed on only 11 of the 21 tumor specimens, because the other frozen specimens were not available for this analysis. The PCR products were visualized with ethidium bromide staining and clearly appeared as the band of interest at 283 bp (Fig. 3). The expression of MDR-1 mRNA was clearly seen in eight of the 11 (72.7%) specimens examined by RT-PCR assay. Weak expression was detected in the other three specimens using an image analyzing system. The expression was semiquantitatively determined with β actin mRNA (93 bp) as the internal control. The values were significantly higher in the Pgp-positive group (0.92 ± 0.33) than in the Pgp-negative group (0.40 ± 0.13) (p = 0.0253). This result indicated that Pgp was regulated through MDR-1 mRNA expression, and that Pgp levels were increased with greater expression of MDR-1 mRNA.

IV. Correlation between 99mTc-MIBI SPECT and Pgp or MDR-1 mRNA expression

The RI of 99mTc-MIBI SPECT in Pgp-positive cases (−9.12 ± 22.27%) was significantly lower than that in Pgp-negative cases (28.79 ± 22.80%) (p = 0.0016, Table 3). The RI of 99mTc-MIBI SPECT in cases with high MDR-1 mRNA expression (MDR-1 mRNA/β actin mRNA ≥ 0.5) (0.91 ± 18.96%) was also significantly lower than that in cases with low MDR-1 mRNA expression (MDR-1 mRNA/β actin mRNA < 0.5) (37.05 ± 27.63%) (p = 0.0291). There was a linear correlation between RI and MDR-1 mRNA/β actin mRNA (r = 0.601, p = 0.494).

Table 3 Single photon emission computed tomography (SPECT) characteristics and P-glycoprotein expression

<table>
<thead>
<tr>
<th>P-glycoprotein staining</th>
<th>99mTc-MIBI SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>DR</td>
</tr>
<tr>
<td>Positive (n = 14)</td>
<td>1.91 ± 0.86</td>
</tr>
<tr>
<td>Negative (n = 7)</td>
<td>1.56 ± 0.25</td>
</tr>
</tbody>
</table>

Values are mean ± standard error. *p = 0.0016. DR: delayed uptake ratio, ER: early uptake ratio, RI: retention index, 99mTc-MIBI: technetium-99m sestamibi.

Discussion

The present study found no relationship between 99mTc-MIBI SPECT findings and histological malignancy or proliferative potential in meningiomas. However, the 99mTc-MIBI SPECT findings were inversely correlated with the expression of Pgp.

This study used the pituitary gland as the normal control because of the physiological and constant characteristics. Meningiomas usually show high 99mTc-MIBI uptake because of the absence of the blood-brain barrier and the hypervascularity, whereas 99mTc-MIBI uptake is minimum in normal brain tissue due to the blood-brain barrier. In this study, use of the contralateral normal brain tissue as a control for 99mTc-MIBI SPECT resulted in extraordinarily high values for the T/N ratio in meningiomas. Evaluation of the tumor uptake/normal pituitary gland uptake ratio provides more reliable evaluation of the tumor viability, especially in meningiomas.

99mTc-MIBI SPECT can predict the response to chemotherapy in cases of malignant tumors because decreased accumulation of 99mTc-MIBI implies the presence of Pgp, which also transports chemotherapeutic agents outward from the tumor cell. MDR-1 gene expression occurs in gliomas and other tumors. Study of 99mTc-MIBI SPECT and MDR-1 gene expression in six gliomas found that four patients with 99mTc-MIBI SPECT concordance

Neurol Med Chir (Tokyo) 43, December, 2003
had tumors without MDR-1 gene expression, whereas two patients with 99mTc-MIBI SPECT discordance had tumors with MDR-1 gene expression, indicating that 99mTc-MIBI SPECT is a non-invasive method for detecting MDR-1 gene expression in gliomas.10 In contrast, Pgp expression of both tumor cells and vascular endothelial cells showed no correlation with MIBI SPECT findings in 26 gliomas.32 Pgp was expressed in the tumor cells but not in the endothelial cells of four cases of meningiomas.30

Pgp and other types of drug resistance-related gene, such as multidrug resistance-associated protein (MRP) and O6-methylguanine-DNA methyltransferase, are highly expressed in meningiomas.7,10,14,34,36 Our study revealed that Pgp was expressed in 14 of 21 (66.7%) meningiomas, MDR-1 mRNA in eight of 11 (72.7%) meningiomas, and that the RI of 99mTc-MIBI SPECT was correlated significantly with both Pgp and MDR-1 mRNA expression. These results indicate that Pgp, an MDR-1 gene product, contributes to the washout mechanism of 99mTc-MIBI. In this study, the washout rate was defined as the difference in uptake ratio between 15 minutes and 3 hours after injection of 99mTc-MIBI. It is not known whether the Pgp-mediated transport of radioactivity is a rapidly functioning mechanism or not, so Pgp transport may be already completed within 15 minutes of injection of 99mTc-MIBI. 99mTc-MIBI is a rapidly functioning mechanism or not, so Pgp whether the Pgp-mediated transport of radioactivity may be already completed within 15 minutes of injection of 99mTc-MIBI. 99mTc-MIBI is a substrate for both Pgp and the MRP. Therefore, the retention of MIBI in cells may depend on both Pgp and MRP expression, so further studies about the association between retention measured by 99mTc-MIBI SPECT and MRP expression in meningiomas are necessary.

Meningiomas are generally clinically benign, but some cases may be incompletely excised or may recur. Therefore, the tumor response to chemotherapy treatment is important to predict in recurrent, unresectable, or malignant meningiomas. Adjuvant chemotherapy to control the growth of recurrent or unresectable meningiomas with chemotherapeutic agents such as cyclophosphamide, Adriamycin, vincristine, or interferon α has only achieved a low response rate.6,22 Resistance to anticancer drugs such as vincristine, etoposide, doxorubicin, and methotrexate is thought to be associated with Pgp expression, so characterization of its expression in meningioma may be important for the prognosis of chemotherapy efficacy.10,33 Little is known about the relationship between Pgp or MDR-1 mRNA expression and the response rate to chemotherapy in meningiomas. Recently, hydroxyurea, a ribonucleotide reductase inhibitor, was used in adjuvant chemotherapy for patients with recurrent or unresectable meningioma, and was effective in halting the growth of enlarging benign meningiomas but not malignant meningiomas.21,28,31 Hydroxyurea may inhibit the growth of meningioma cell lines through an apoptotic mechanism.30 Interestingly, in vitro exposure of renal cancer cells to low-dose hydroxyurea causes loss of chromosomal aberration, decrease in the number of MDR-1 gene copies, and increased sensitivity to vinblastine.13

Our findings indicate that 99mTc-MIBI SPECT, although not useful to determine the proliferative potential, could predict whether meningiomas, especially recurrent or unresectable meningiomas, overexpress Pgp or MDR-1 mRNA which may be an important factor in the sensitivity or resistance to anticancer drugs.

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Commentary on this paper appears on the next page.
Commentary

The authors attempted to identify any correlation of 99mTc-MIBI SPECT findings with histological malignancy, proliferative potential and the expression of MDR-1 in meningiomas. They found that 99mTc-MIBI findings were inversely correlated with the expression of MDR-1. This result is consistent with the previous data that 99mTc-MIBI can predict the response to chemotherapy in various malignant tumors since MDR-1 drug resistant protein may be involved in transportation of 99mTc-MIBI from the tumor cells.1–3) The authors need to perform further experiments to determine whether the levels of MDR-1 expression really correlate with chemoresistance in meningioma cells. If they can clarify this point in the future, the information in this manuscript may be useful for considering chemotherapeutic approaches for patients with inoperable meningioma.

References


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Technetium-99m labeled methoxyisobutylisonitrile (MIBI) is a rather new tracer, which can be a substrate for Pgp. Therefore, the authors evaluated the 99mTc-MIBI uptake index of meningioma in relation to Pgp, MDR-1 mRNA and MIB-1 labeling index. They identified no relationship between 99mTc-MIBI uptake and MIB-1 labeling index or histological malignancy of meningioma. However, they found a positive correlation between Pgp and 99mTc-MIBI uptake. The meaning of 99mTc-MIBI uptake is still controversial. Some reports indicated that 99mTc-MIBI uptake is directly correlated with the malignancy of the tumor, but others indicated no correlation. The authors' approach is scientific and the results are reasonable. This report shows the potential of MIBI or MIBI-related compounds as an indicator of Pgp or MDR-1.

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