IV. 8 **Differential Diagnosis between Hepatocellular Carcinoma and Metastatic Liver Tumor Using 2-Deoxy-2-(¹⁸F)Fluoro-D-Galactose with Positron Emission Tomography**

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**Introduction**

Galactose is one of the main constituents of glycoprotein and glycolipid, and is metabolized mainly in the liver for adults. 2-deoxy-2-(¹⁸F)fluoro-D-galactose (¹⁸F-FDGal), a positron emitting galactose analogue¹,², accumulated mainly in the liver, and its accumulation of liver was suppressed by galactose preloading³,⁴. Using this character, ¹⁸FDGal was applied for evaluation of liver function and represented that the accumulation of ¹⁸FDGal in the cirrhotic liver was lower than that in the normal liver.⁵,⁶ In this study, we proposed this tracer as a differential diagnostic agent between hepatocellular carcinoma (HCC) and metastatic liver tumor using positron emission tomography (PET).

**Method and Materials**

1. **Radiopharmaceuticals**

  2-deoxy-2-(¹⁸F)fluoro-D-galactose (¹⁸FDGal) were synthesized by the method developed by Tada et al.¹,². Chemical purity was more than 98% and specific activity was 7-12 mCi at the end of procedure. Quality assurance tests of ¹⁸FDGal for clinical use were performed according to safety guideline of the clinical research committee of Tohoku University.

2. **Clinical study**

  Clinical studies were performed on 6 patients with hepatocellular carcinoma (HCC) and 5 patients with metastatic liver tumor (4 colon cancer, 1 gall bladder cancer, and 1 lung cancer) using positron emission tomography (ECAT II, Ortec). Table 1 shows the patient profiles. The diagnosis of all cases was confirmed using ultrasonic echogram, X-CT, angiography, biopsy,
tumor maker, and clinical course. The tumor size was measured by X-ray CT. The resolution of the system in this study was 15 mm (full width half maximum) using medium resolution shadow shield. Transmission scan was performed using 1.2 mCi $^{68}$Ge/$^{68}$Ga ring source before $^{18}$FDGAl injection. Two mCi of $^{18}$FDGAl was injected to the cubital vein. After injection of $^{18}$FDGAl, sequential liver scanning was performed every 5 min for a period of 45 min and one or two scans of another location of the liver was added. Emission scans were corrected for decay and attenuation.

3. Evaluation of $^{18}$FDGAl accumulation to the tumor

The 11 mm x 11 mm of ROIs were set in the tumor and the surrounding livers to obtain radioactivities. A differential absorption ratio (D.A.R.) was used as an indicator of accumulation of $^{18}$FDGAl to the tumor and the liver.

$$DAR = \frac{ECAT\ count \times \ calibration\ factor}{injection\ dose\ (mCi)/body\ weight\ (kg)}$$

Results

Table 2 showed the PET findings and the D.A.R. value at 45 min after $^{18}$FDGAl injection. HCC showed positive or negative images according the surrounding liver accumulation. Every metastatic liver tumor showed negative images until study period. The mean D.A.R. at 45 min after injection of HCC is 17.1(±2.27), and metastatic liver tumor is 4.4(±1.24) with significant differences (p<0.01 Student t-test).

Figure 1 showed the time course of mean DAR of HCC and metastatic liver tumor. $^{18}$FDGAl accumulated in HCC gradually, and the accumulation reached plateau state at 30 min after injection. The accumulation of metastatic liver tumor reached the plateau state at 10 min after $^{18}$FDGAl injection. The mean DAR of HCC is higher than that of metastatic liver tumor in every sequential scans significantly (p<0.01 Student t-test).

Case 1. A 72-year-old man with a history of liver cirrhosis was admitted with hypochondralgie. An ultrasonic echogram revealed abnormal mass in the liver. An X-ray computerized tomographic scan (X-CT) showed abnormal mass in the left lobe of the liver (4.0 x 3.3 x 3.8 cm) (Fig. 2a). Angiographical findings suggested hepatocellular carcinoma which mass size continued to grow against an anti-cancer therapy. (VP-16 1950 mg, interferon $9 \times 10^6$JRU) $^{18}$F-FDGAl image at 5 minutes after injection showed a high accumulation in the tumor, but gradually the accumulation to the surrounding liver was increased, and finally the accumulation of the surrounding liver was almost the same to the tumor (Fig. 2b). DARs of tumor and the surrounding liver at 45 min after $^{18}$FDGAl was 18.3(±1.50) and 16.3(±1.06).

Case 2. A 43-year-old man was admitted with dyspnea and chest pain. X-ray plane film and X-CT showed abnormal mass in the left upper lobe of the
lung. Sputa cytology represented large cell carcinoma in the lung. Hematological findings showed aplastic anemia. Radiation therapy and chemotherapy were performed, but because of aplastic anemia, these therapy were discontinued. Two month after stopping the therapy, X-CT and echogram showed abnormal mass in the right lobe of the liver (Fig. 3a). PET study using $^{18}F$DGal was performed 1 month before the death caused by respiratory failure. Metastatic lesion in the liver represented negative image during the study period (Fig. 3b). DARs of tumor and the surrounding liver at 45 min after injection were $5.7 \pm 0.31$ and $25.8 \pm 1.41$. Autopsy was performed, and the metastatic lesion in the liver consisted by viable tumor cells macroscopically.

Discussion

The technical development of imaging methods improved the detecting ability of tumor in the liver. These methods were confined in the existence diagnosis but did not reach quantitative diagnosis. In the field of nuclear medicine, $^{99m}Tc$ neoglycoprotein which was the indicator of asialaialoglycoprotein receptor was developed, and evaluated for clinical usefulness about the liver disease$^{9-13}$ but it represented negative images about HCC.$^{11}$ Therefore it was very hard to differentiate between HCC and metastatic liver tumor. In this meanings, $^{99m}Tc$ neoglycoprotein has same potential as $^{99m}Tc$-phytate about the differential diagnosis between HCC and metastatic liver tumor.

$^{18}F$DGal which we used in this study is a positron emitting galactose analogue$^{1,2}$, and expressed as a quantitative galactose metabolism imaging tracer.$^{3-6}$ On this clinical studies, we used this tracer to differentiate between HCC and the metastatic liver tumor.

HCC images with PET using $^{18}F$DGal showed positive and negative images according to the $^{18}F$DGal accumulation of the surrounding liver. But DAR of HCC at 45 min after injection is higher than that of and metastatic liver tumor significantly. It is reported that FDGal was FDGal-l-phosphate and trapped UDP-FDGal in the experimental liver tumor and the liver.$^{14-16}$ Bauer reported that galactokinase activity was preserved in the experimental liver tumor.$^{17}$ These suggested that the high $^{18}F$DGal accumulation of HCC caused by the preservation of galactokinase activity in HCC. Though DAR of HCC limited within a higher range than the metastatic liver tumor, it was scattered in each cases. It reflected the biological difference of HCC, and may correspond to histological difference of HCC.

In our study, DAR of surrounding liver in the metastatic liver tumor cases represented lower than that of normal cases.$^{5,6}$ This may caused by small metastasis which cannot detect using X-CT and ultrasonic echogram, or by the side effect of anticancer drug to the hepatocyte.

From the detection view of liver tumor, our result is less useful than that of recent imaging technique of the liver. But the result of this study
suggested that $^{18}$F-FDGAL is useful for the differential diagnosis of HCC and metastatic liver tumor from the view of quantitative diagnosis.

References

Table 1. Patient list.

<table>
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<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis (primary site)</th>
<th>Complication</th>
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<tr>
<td>1</td>
<td>52</td>
<td>M</td>
<td>HCC*</td>
<td>Orbital metastasis, Liver cirrhosis</td>
<td>Solitary: 11.6 x 15.3 x 12.5</td>
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<td>2</td>
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<td>3</td>
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<td>4</td>
<td>35</td>
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<td>Polycythemia Vera</td>
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<tr>
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<td>Chronic hepatitis</td>
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<td>6</td>
<td>58</td>
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<td>HCC</td>
<td>Chronic hepatitis</td>
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<tr>
<td>7</td>
<td>55</td>
<td>F</td>
<td>MLT** (Colon)</td>
<td>Lung and cerebellum metastasis</td>
<td>Multiple: 6.4 x 15.3 x 7.5</td>
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<td>8</td>
<td>43</td>
<td>M</td>
<td>MLT (Lung)</td>
<td>Aplastic anemia</td>
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<td>9</td>
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<td>Pancreas metastasis</td>
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<td>Multiple: 5.1 x 5.1 x 6.2</td>
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<tr>
<td>11</td>
<td>74</td>
<td>F</td>
<td>MLT (Colon)</td>
<td></td>
<td>Multiple: 4.4 x 4.4 x 6.2</td>
</tr>
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</table>

* HCC: Hepatocellular carcinoma
** MLT: Metastatic liver tumor

Table 2. PET findings and DAR of 18F-FDGaI.

<table>
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<th>Tumor finding on PET</th>
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<td>last image***</td>
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<td>HCC 1</td>
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</tr>
<tr>
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<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Mean (±S.D.) 17.1 ± 2.27% 19.9 ± 5.56

MLT** 7  | Negative | Negative | 4.8 ± 1.68 | 17.1 ± 1.07 |
| 8  | Negative | Negative | 5.7 ± 0.31 | 25.0 ± 1.41 |
| 9  | Negative | Negative | 5.3 ± 1.30 | 17.2 ± 1.47 |
| 10 | Negative | Negative | 3.4 ± 0.98 | 16.5 ± 1.96 |
| 11 | Negative | Negative | 2.8 ± 0.47 | 19.9 ± 0.80 |

Mean (±S.D.) 4.4 ± 1.25 19.3 ± 3.86

* DAR (Differential absorption ratio) at 45 min after 18F-FDGaI injection
** PET image obtained during first 5 min after 18F-FDGaI injection
*** PET image obtained during 40 min to 45 min after 18F-FDGaI injection

* HCC: Hepatocellular carcinoma
** MLT: Metastatic liver tumor

$ p<0.01$ (Student's t-test)
Fig. 1. Time activity curve of HCC and metastatic liver tumor using $^{18}$FDGal. Isotope accumulation to HCC was higher than metastatic liver tumor in every sequential scans significantly. (p<0.01 Student t-test)
Fig. 2. A case of HCC. 2b showed time course images with $^{18}_\text{FDG}$Gal using PET, and 2a presented the X-CT image at the same level. High accumulation to HCC was observed first 5 min scan, but because of the accumulation of surrounding liver, the tumor border became unclear gradually.
Fig. 3. A case of metastatic liver tumor (lung cancer, large cell). 3b showed time course images with $^{18}$FDGAl using PET, and 3a presented the X-CT image at the same level. Tracer accumulation to the metastatic liver tumor was lower than surrounding liver during study period.