CLINICAL RESEARCH
57. Experiences of Carbon Ion Radiotherapy at NIRS

Hirohiko Tsuji, Shinroku Morita, Tadaaki Miyamoto, Jun-etsu Mizoe, Tadashi Kamada, Hiroshi Kato, Hiroshi Tsuji, Shigeru Yamada, Naotaka Yamamoto and Hajime Murata

Keywords: carbon ion radiotherapy, HIMAC, heavy ion

Functional and cosmetic preservation is of paramount importance in cancer therapy. For this purpose, heavy ion therapy is an advantageous modality over megavoltage x-ray therapy in terms of safely delivering high doses coupled with increased cell-killing ability. Heavy ions have the beneficial property of superior physical dose localization due to exhibiting the Bragg peak in the body, as well as greater biological effectiveness than low-LET radiation (protons and photons). Thus, heavy ions are expected to be effective against locally advanced radio-resistant tumors and those located near critical structures. In 1993, construction and installation of the Heavy Ion Medical Accelerator in Chiba (HIMAC), the world's first heavy ion accelerator complex dedicated to medical use in a hospital...

Table 2. Patient Distribution registered in Carbon Ion Therapy at NIRS
(Treatment: June 1994 to August 2001)

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>9</td>
<td>10</td>
<td>19</td>
<td>31</td>
<td>22</td>
<td>38</td>
<td>29</td>
<td>20</td>
<td>178</td>
</tr>
<tr>
<td>Brain</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>6</td>
<td>9</td>
<td>7</td>
<td>15</td>
<td>4</td>
<td>65</td>
</tr>
<tr>
<td>Base of skull</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Lung</td>
<td>6</td>
<td>11</td>
<td>27</td>
<td>17</td>
<td>28</td>
<td>33</td>
<td>45</td>
<td>20</td>
<td>187</td>
</tr>
<tr>
<td>Liver</td>
<td>-</td>
<td>12</td>
<td>13</td>
<td>19</td>
<td>25</td>
<td>17</td>
<td>22</td>
<td>11</td>
<td>119</td>
</tr>
<tr>
<td>Prostate</td>
<td>-</td>
<td>9</td>
<td>18</td>
<td>10</td>
<td>30</td>
<td>30</td>
<td>31</td>
<td>16</td>
<td>144</td>
</tr>
<tr>
<td>Uterus</td>
<td>-</td>
<td>9</td>
<td>13</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>13</td>
<td>2</td>
<td>69</td>
</tr>
<tr>
<td>Bone/ soft tissue</td>
<td>-</td>
<td>9</td>
<td>13</td>
<td>19</td>
<td>18</td>
<td>25</td>
<td>7</td>
<td>91</td>
<td>41</td>
</tr>
<tr>
<td>Esophagus</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>16</td>
<td>4</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td>Pancreas (pre-op RT)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>0.6</td>
</tr>
<tr>
<td>Rectum (Pelvic rec)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Eye (advanced)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>-</td>
<td>24</td>
<td>16</td>
<td>30</td>
<td>17</td>
<td>32</td>
<td>14</td>
<td>5</td>
<td>138</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>83</td>
<td>126</td>
<td>159</td>
<td>168</td>
<td>188</td>
<td>201</td>
<td>96</td>
<td>1042</td>
</tr>
</tbody>
</table>

Table 3. Normal tissue morbidity in carbon ion therapy at NIRS
(Treatment: June 1994 to August 2001)

<table>
<thead>
<tr>
<th>Site</th>
<th>Early (&lt;3mo)</th>
<th>Late (&gt;3mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalp</td>
<td>77</td>
<td>22</td>
</tr>
<tr>
<td>Head &amp; neck</td>
<td>180</td>
<td>2</td>
</tr>
<tr>
<td>Chest</td>
<td>206</td>
<td>0</td>
</tr>
<tr>
<td>Upper abdomen</td>
<td>128</td>
<td>10</td>
</tr>
<tr>
<td>Lower abdomen</td>
<td>212</td>
<td>154</td>
</tr>
<tr>
<td>Others</td>
<td>243</td>
<td>143</td>
</tr>
<tr>
<td>Total</td>
<td>1046</td>
<td>204</td>
</tr>
<tr>
<td>(%)</td>
<td>(100)</td>
<td>(20)</td>
</tr>
<tr>
<td>Mucosa</td>
<td>168</td>
<td>24</td>
</tr>
<tr>
<td>Lung</td>
<td>252</td>
<td>234</td>
</tr>
<tr>
<td>Intestine</td>
<td>512</td>
<td>431</td>
</tr>
<tr>
<td>Bladder/Urethra</td>
<td>235</td>
<td>194</td>
</tr>
</tbody>
</table>
environment, was completed at NIRS. The HIMAC project was initiated as part of the Japanese government's 10-year plan to combat cancer. In June 1994, clinical research for the treatment of malignant tumors was begun using carbon ions generated by the HIMAC. Since then more than 1,000 patients have been treated with carbon ions, in which both the phase I/II dose escalation study and phase II study were performed.

Table 2-5 summarize the results of carbon ion radiotherapy including the radiation-induced morbidity, local control, and survival rates for patients with various types of tumors.

Table 4. Results of carbon ion radiotherapy at NIRS (Treatment: June 1994 to August 2001)

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Phase</th>
<th>Material</th>
<th>Treatment (fractions/week)</th>
<th>No. of patients</th>
<th>Response rate a)</th>
<th>2yr local control b)</th>
<th>3yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;N-1</td>
<td>I/II</td>
<td>Locally advanced</td>
<td>18/6</td>
<td>17</td>
<td>73%</td>
<td>80%</td>
<td>44%</td>
</tr>
<tr>
<td>H&amp;N-2</td>
<td>I/II</td>
<td>Locally advanced</td>
<td>16/4</td>
<td>19</td>
<td>68%</td>
<td>71%</td>
<td>44%</td>
</tr>
<tr>
<td>H&amp;N-3</td>
<td>II</td>
<td>Locally advanced</td>
<td>16/4</td>
<td>134</td>
<td>52%</td>
<td>61%</td>
<td>42%</td>
</tr>
<tr>
<td>Lung-1</td>
<td>I/II</td>
<td>Stage I (peripheral)</td>
<td>18/6</td>
<td>47(+1)</td>
<td>54%</td>
<td>62%</td>
<td>88%</td>
</tr>
<tr>
<td>Lung-2</td>
<td>I/II</td>
<td>Stage I (peripheral)</td>
<td>9/3</td>
<td>34</td>
<td>85%</td>
<td>86%</td>
<td>65%</td>
</tr>
<tr>
<td>Lung-3</td>
<td>I/II</td>
<td>Stage I (Hilar)</td>
<td>9/3</td>
<td>10</td>
<td>90%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Lung-4</td>
<td>II</td>
<td>Stage I (peripheral)</td>
<td>9/3</td>
<td>50(+1)</td>
<td>65%</td>
<td>100%</td>
<td>73%</td>
</tr>
<tr>
<td>Lung-6</td>
<td>I/II</td>
<td>Stage I (peripheral)</td>
<td>4/1</td>
<td>18</td>
<td>67%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Liver-1</td>
<td>I/II</td>
<td>T2~4 MONO</td>
<td>15/5</td>
<td>24(+1)</td>
<td>75%</td>
<td>79%</td>
<td>50%</td>
</tr>
<tr>
<td>Liver-2</td>
<td>I/II</td>
<td>T2~4 MONO</td>
<td>4<del>12</del>1~3</td>
<td>82(+4)</td>
<td>72%</td>
<td>83%</td>
<td>45%</td>
</tr>
<tr>
<td>Liver-3</td>
<td>II</td>
<td>T2~4 MONO</td>
<td>4/1</td>
<td>11</td>
<td>55%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prostate-1</td>
<td>I/II</td>
<td>B2~C</td>
<td>C ion+Hormone</td>
<td>35</td>
<td>-</td>
<td>100%</td>
<td>94%</td>
</tr>
<tr>
<td>Prostate-2</td>
<td>I/II</td>
<td>A2~C</td>
<td>C ion+Hormone</td>
<td>61</td>
<td>-</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>Prostate-3</td>
<td>II</td>
<td>T1C~C</td>
<td>C ion+Hormone</td>
<td>47</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Uterus-1</td>
<td>I/II</td>
<td>III-Iva(ACC)</td>
<td>24/6</td>
<td>30</td>
<td>100%</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Uterus-2</td>
<td>I/II</td>
<td>lib-Iva(SCC)</td>
<td>24/6</td>
<td>14</td>
<td>100%</td>
<td>67%</td>
<td>36%</td>
</tr>
<tr>
<td>Uterus-3</td>
<td>I/II</td>
<td>lib-Iva(SCC)</td>
<td>20/5</td>
<td>11</td>
<td>100%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Uterus</td>
<td>II</td>
<td>Advanced(Adenoca)</td>
<td>20/5</td>
<td>12</td>
<td>100%</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td>Bone/SOFT-1</td>
<td>I/II</td>
<td>un-resectable</td>
<td>16/4</td>
<td>57(+7)</td>
<td>36%</td>
<td>77%</td>
<td>50%</td>
</tr>
<tr>
<td>Bone/SOFT-2</td>
<td>II</td>
<td>un-resectable</td>
<td>16/4</td>
<td>30(+1)</td>
<td>57%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a) Response rate : Percent of tumors with >50% reduction in size.
b) Local control rate : Percent of tumors with no evidence of local recurrence or relapse.

Table 5. Clinical studies for Stage I NSCLC

<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Lung-1 (9303)</th>
<th>Lung-2 (9701)</th>
<th>Lung-3 (9801)</th>
<th>Lung-4 (9802)</th>
<th>Lung-6 (0001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>I/II</td>
<td>I/II</td>
<td>I/II</td>
<td>II</td>
<td>I/II</td>
</tr>
<tr>
<td>Period of the study</td>
<td>10/'94 to 9/'97</td>
<td>9/'97 to 2/'99</td>
<td>4/'98 to 4/'99</td>
<td>4/'99 to 12/'00</td>
<td>12/'00 to 12/'00</td>
</tr>
<tr>
<td>Tumor Type</td>
<td>All type*</td>
<td>Peripheral</td>
<td>Central</td>
<td>Peripheral</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Total Dose (GyE)</td>
<td>59.4~95.4</td>
<td>68.4~79.2</td>
<td>57.6~64.8</td>
<td>72</td>
<td>54 or 60</td>
</tr>
<tr>
<td>Fraction / wks (fixed)</td>
<td>18f/6w</td>
<td>9f/3w</td>
<td>9f/3w</td>
<td>9f/3w</td>
<td>4f/1w</td>
</tr>
<tr>
<td># Pats (# Tumors)</td>
<td>47(48)</td>
<td>34(34)</td>
<td>15(15)</td>
<td>50(51)</td>
<td>35(35)</td>
</tr>
<tr>
<td>Adenoca / SCC</td>
<td>26/22/0</td>
<td>18/15/1</td>
<td>13/2/0</td>
<td>32/19/0</td>
<td>23/11/1</td>
</tr>
</tbody>
</table>

* All type includes both peripheral and central type of tumor.
58. The Dose - Volume Histogram Analysis for Pelvic Tumor Using Carbon Ion Radiotherapy

Takeshi Yanagi, Tadashi Kamada, Hiroshi Tsuji, Shigeru Yamada and Hirohiko Tsuji

Keywords: carbon ion radiotherapy, pelvic tumor

It is important to conform an irradiation beam only to a tumor, and to minimize the dose to the normal tissues around it. International interests exist in the use of charged particles in cancer radiotherapy, because of its good dose distribution. The aim of this study is to confirm the merits of the dose distribution of carbon ion beams compared to photon beams by simulating treatment planning analyzed by dose volume histograms (DVHs).

In comparative treatment planning, two types of pelvic tumor were selected; case 1/sacrum chordoma (volume: 701ml) and case 2/ recurrent rectal cancer (2267ml). Plans for of carbon and conventional photon beams were simulated using CT scans for each pelvic tumor, and the results were analyzed using DVH. In standard photon planning, 3,4,5,7 ports were used in case 1, and 2,3,4,5,6 ports in case 2, and the margin for the planning target volume (PTV) was given to cover the clinical target volume (CTV) with 80 - 100% of the prescribed dose. In carbon planning, 3 ports were used, and the minimum target dose given was at least 90% of the prescribed dose.

As a result, for the target volume, the carbon plans provided good coverage with a homogeneous dose around the maximum dose in both cases. Volumes of both bowels and bladders could be reduced at any dose levels in the carbon plans. Whole irradiated volumes of each case were less at low or middle dose level for carbon ion beams than for photons. Significantly higher dose could be given to 95% of the target with carbon beams than in photons for the bowel dose <50GyE. The use of carbon ion beams provided improved target dose homogeneity and reduced doses to critical structures compared to conventional photon beams.

The use of carbon ion beams provides superior dose localization characteristics to those of photons.

2 Motojima General Hospital

Key words: second cancer, radiation therapy, cervical carcinoma

Purpose: To examine the incidence and clinical feature of second cancer following radiation therapy.

Materials and methods: Between 1961 and 1990, 1877 patients with uterine cervical squamous cell carcinoma were treated radically with radiation therapy alone at NIRS. Patients were followed up intensively; 10 years after radiation therapy the follow up rate was more than 90%. We diagnosed a radiation-associated second cancer using the following criteria: (1) difference of histologic type from the primary cancer (except for vagina); (2) latency period of at least 2 years after radiation therapy (RT); and (3) development site in the irradiated field.

Results: Twenty-nine of 1877 (1.54%) patients developed second cancer. The sites of second cancer were rectum in 8 patients, bladder in 3, uterus in 6, ovary in 5, vagina in 2, and bone and soft tissue in 5. Patient age at diagnosis of cervical carcinoma was 40 to 75 years, with a median of 58 years and at diagnosis of second cancer was 49 to 95 years, with a median of 72 years. Latency period from RT to the development of second cancer ranged from 3 to 27 years, with a median of 16 years. Treatment of second cancer consisted of surgery in 12 patients (41%), RT in 4 (14%), and chemotherapy in 1 (3%). Median survival from the diagnosis of second cancer was 7 months.

Conclusion: Radiation therapy for cervical carcinoma results in large numbers of long term survivors who can develop second cancers very late in life. The advantage of radiation therapy may be considered large enough to compensate for the risk of radiation-associated cancer.

60. Usefulness of 3D Ultrasonography in Diagnosis of Hepatocellular Carcinoma and Its Invasively Growing Lesion: Deciding a Precise Target Volume in Radiation Therapy

Hiroshi Tsuji, Hirohiko Tsuji

Keywords: hepatocellular carcinoma, ultrasonography, Fusion 3D, contrast-enhanced Fusion 3D, contrast-enhanced CT scan

One half of local recurrences of hepatocellular carcinomas (HCC) treated with carbon ion therapy occurred in the tumors that had invasively growing parts in themselves. Vascular invasion is one of the most clinically problematic findings in HCC treatment.
Therefore, more precise examination of invasively growing lesions is essential to advance clinical results in HCC treatment.

Ultrasonography (US) is an examination offering easy observation of the local environment and providing vascular information around the HCC. So, in 1995 we started the study of US for diagnosis of HCC, especially for diagnosis of both tumors and vascular structures with ultrasonographic three-dimensional images (Fusion 3D). We also started a study of Fusion 3D using a contrast agent (contrast-enhanced Fusion 3D). The US machine we used was an Aplio (Toshiba Medical Systems Co., Ltd.) and contrast agent was Levovist (Nihon Schering KK).

We investigated the characteristic features of HCC, including the usefulness of contrast-enhanced Fusion 3D in diagnosis of invasively growing lesions of HCC.

**Study 1: Characteristic features of HCC in contrast-enhanced Fusion 3D**

We performed contrast-enhanced Fusion 3D on 22 patients with histologically proven HCC (40mm or less in diameter) and 5 with metastatic liver cancer. The results were as follows. 1. We recognized a Network Pattern and Flush Sign as characteristic features of HCC that were thought to be contrast-enhanced vascular images (Figure and Table). None of these features were detected in the metastatic liver cancers. 2. All five HCCs 15mm or less in diameter had the Network Pattern and Flush Sign, 60% of which had early staining and 40% had late washout in the contrast-enhanced CT scan.
with bolus injection of a contrast agent.

**Study 2: Diagnosis of invasively growing lesions of HCC with contrast-enhanced Fusion 3D**

We performed contrast-enhanced Fusion 3D on 41 patients with histologically proven HCC. The results were as follows. 1. All the invasively growing lesions of HCC had the Network Pattern and Flush Sign. 2. We could detect the invasively growing lesions of HCC with contrast-enhanced Fusion 3D more easily than simple US for both 2D and 3D. 3. HCC's 15mm or less in diameter had no invasively growing lesions, 74% of HCCs more than 15mm in diameter had the lesions. 4. Sixty-seven percent of the invasively growing lesions detected with Contrast-Enhanced Fusion 3D could not be diagnosed by contrast-enhanced CT scan.

In conclusion, contrast-enhanced Fusion 3D may allow the diagnosis of HCC and its invasively growing lesions by such characteristic features as the Network Pattern and Flush Sign, and it may be superior to the contrast-enhanced CT scan especially in small HCC.

**61. Cytokine Responses Detected in Blood from Cancer Patients Given X-ray or Carbon Ion Therapy**

Shigeru Yamada, Tadashi Kamada and Hiroshi Tsujii.

*Keywords: x-ray therapy, carbon ion therapy, cytokines*

Ionizing radiation induces an acute inflammatory response in many normal cells and tissues. Exposure of cells to irradiation induces some cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Heavy ions are reported to have several advantages compared to conventional photon therapy, including a better physical dose distribution and a higher biological efficiency in tumor cell killing. However there are few data on biological responses in patients treated with heavy ions compared to photon therapy. In this study we examined cytokine responses induced by carbon ions and X-ray irradiation. We measured inflammatory cytokines such as IL-4, IL-6, IL-8, TNF-α and INF-γ. Blood samples from patients with esophageal cancer were obtained before and after treatment. No significant differences in the response of these cytokines from the patients treated with X-rays were detected. On the other hand IL-4, IL-8 and TNF-α displayed similar response with X-rays, however the secretion of IL-6 and INF-γ was induced by the carbon ions. These results suggested cytokine responses differ between X-rays and carbon ions.

**62. Objective Assessment of Cranial Nerve Neuropathy by Heavy Ions**

Azusa Hasegawa, Jun-etsu Mizoe, Hitoshi Miyachi, Shogo Hasegawa, Atsushi Mizota and Hirohiko Tsujii

*Keywords: heavy ion therapy, neuropathy, carbon ion radiotherapy*

Purpose: In radiation therapy of head and neck cancers, preservation of the Quality Of Life (QOL) is important for patients. Therefore, we evaluated the late effects of carbon ions on the cranial nerve neuropathy as the start for an investigation on safe doses for the cranial nerves. These results are a clinical indicator of the QOL.

Patients and Methods: We selected patients whose trigeminal and/or optic nerves were included in Planning Target Volume (PTV), and we recorded somatosensory evoked potentials before and after carbon ion radiotherapy.

1. **Visual Evoked Potential (VEP)**
   The time-course VEP recording and examination of visual acuity were performed for patients who developed a loss of visual acuity due to tumor invasion. We objectively investigated nerve stimulation using VEP during carbon ion irradiation, and we reconsidered the treatment plan if the nerve pathway is included in the irradiation field.

2. **Trigeminal Somatosensory Evoked Potential (TSEP)**
   TSEP was recorded to examine the clinical availability for patients with/without paresthesia at the time of carbon ion radiotherapy. The stimulating electrodes were composed of a spring clip with upper and lower lips. For patients who were expected to show nerve impairment after irradiation, we recorded the time-course TSEP, and analyzed paresthesia grade.

Results: We are currently still collecting data. This study will be helpful in evaluation of the cranial nerve neuropathy. We present one example case of trigeminal nerve included in PTV. A twenty year-old man was treated using carbon ion radiotherapy. After six months, the early components corresponded with the latency of the normal TSEP (Fig. 27).
63. Allelic Loss of Chromosome 2 in Human Oral Squamous Cell Carcinoma: Correlation with Lymph Node Metastasis

Nobuharu Yamamoto, Jun-etsu Mizoe, Hideyuki Nomasawa, Hidetaka Yokoe, Katsuhiko Uzawa, Takahiko Shibahara, Hirohiko Tsuji, Hiroyasu Noma and Hideki Tanzawa

(NIRS and Tokyo Dental College; Tokyo Dental College; Chiba Univ. Hospital; Chiba Univ.)

To evaluate the role of chromosome 2 deletions in human oral squamous cell carcinoma (SCC) progression and to define the precise location of putative tumor suppressor genes, we examined 40 primary tumors and seven lymph node metastatic tumors from 40 patients with oral SCC by the polymerase chain reaction (PCR)-loss of heterozygosity (LOH) assay, using 10 different polymorphic loci on the long arm of chromosome 2. LOH was observed in 67.5% of the patients at one or more loci on the chromosome 2q. Two commonly deleted regions with high frequency of LOH, D2S1327 region at 2q32-35 (31.6%) and D2S206 region at 2q36 (36.7%), were identified by the deletion mapping of chromosome 2q, suggesting the presence of putative tumor suppressor genes associated with oral SCC. Examination of seven metastatic tumors also revealed four commonly deleted regions, D2S436, D2S1327, D2S155 and D2S164. Of these four regions D2S1327 region had no significant increase in the frequency of LOH between in primary tumors and in metastatic tumors. However, for the other three regions, the frequencies were much increased in metastatic tumors, compared to the results in primary tumors. In particular, very high frequencies of LOH in metastatic tumors were detected at two regions on 2q35, 100.0% at D2S155 and 57.1% at D2S164, suggesting a significant relationship between lymph node metastasis and LOH at these two regions. Our results indicate that LOH on chromosome 2q is a common event in oncogenesis and/or progression of oral SCC, and they also suggest that LOH at 2q35 plays a significant role in the lymph node metastasis.

Keywords: tumor, oral squamous cell carcinoma

64. Clinical Application of Autoactivation PET Imaging Derived from C-12 Ion Radiotherapy and Its Fusion Imaging with Therapy Planning CT.

Kyoosan Yoshikawa, Takehiro Tomitani, Mitsutaka Kanazawa, Tatsuaki Kanai, Katsumi Tamura, Takashi Tomemori, Susumu Kandatsu, Junetsu Mizoe, Fumio Shishido, Hiroshi Fukuda and Hirohiko Tsuji.

Keywords: autoactivation, carbon ion radiotherapy, HIMAC, PET, CT, fusion imaging

Clinical application of PET imaging of auto activation derived from C-12 ion radiotherapy (HIMAC) was studied. It is very important to perform the PET measurements under exactly the same patient positioning as in HIMAC therapy to compare RI distributions. We performed some clinical PET measurements and got superimposed images of PET and CT planning of
HIMAC therapy patients. We tried to use a fitting method, the automatic multi modality image registration method (AMIR method) of the Dr. View applications. In this method, we fitted the transmission images of PET to planning CT images at the start, and then superimposed emission images on the planning CT images. Our fitting results were relatively good. But some problems were identified. The most important one was due to the difference in patients breathing phases between PET examination and CT imaging. The difference of patients breathing phases should cause fitting errors of the fusion images of PET and CT especially in chest and abdominal regions. To confirm this, we investigated a lung cancer patient who received HIMAC therapy with 15.0 GyE dose per fraction, totally 4 fractions (60 GyE). A PET measurement was done immediately after an irradiation. Two sets of CT images were also taken in both expiration phase and inhalation phase. PET fusion images with the two sets of CT images were calculated and compared with each fusion image. The PET fusion image with CT image in the expiration phase resulted in better quality compared to that in the inhalation phase. We think that the breathing phases of PET and CT should be in phase with each other to perform precise fitting of the two modalities.

65. Functional Diagnosis of Cancer Using PET

Kyosan Yoshikawa, Katsumi Tamura, Takashi Tomemori, Noriyu Matsuno, Masahisa Koga, Susumu Kandatsu, Tetsuya Suhara, Kazutoshi Suzuki, Hiroshi Kato, Junetsu Mizoe, Osamu Inoue, Fumio Shishido, Hiroshi Fukuda and Hirohiko Tsuji

Keywords: Positron emission tomography (PET), C-11 methionine, head and neck cancer, hepatocellular carcinoma, breast tumor

Positron emission tomography (PET) can demonstrate increased metabolic activity as visual images, and it provides alternative information for diagnosis that can be used to complement morphological observations. This year, we carried out three studies on (1) the usefulness of methionine PET for evaluation of the therapeutic effect and prognosis in head and neck cancer, (2) the imaging ability of FDG-PET for hepatocellular carcinoma, and (3) the imaging ability of methionine PET for breast tumor. In study (1), 22 cases with head and neck cancer were followed long term (70.3 months maximum) after HIMAC therapy. Kaplan-Maier methods were applied for evaluation of the relation between methionine uptake in the tumor and patient survival rate, and of the relation between the changing rate of tumor methionine uptake and tumor local control rate. Tumor methionine high uptake state before HIMAC therapy seemed to suggest tumor malignancy and high risk of occurring metastasis, i.e. prognosis poor. When tumor uptake decreased a lot after HIMAC therapy, it suggested good tumor local control. In study (2), 38 cases with hepatocellular carcinoma were studied by FDG-PET. We found that when the liver function was more damaged, liver tissue showed higher FDG accumulation. There was no relationship between tumor differentiation level and FDG uptake, and between the change of FDG uptake after HIMAC therapy and the reduction rate of tumor size. Cases that showed high reduction of tumor FDG uptake after HIMAC therapy tended to show reduced AFP level. In study (3), 9 cases with breast tumor were studied by methionine PET. All breast carcinoma showed positive accumulation of methionine. There was no relationship between methionine uptake level and FDG uptake level. We think that methionine PET gives different information about breast tumor, about differentiation between benignancy and malignancy, and about prognosis after treatment etc., in comparison with FDG-PET.

66. The Cancer Functional Diagnosis and the Evaluation of Therapeutic Effects Using Magnetic Resonance Imaging and Spectroscopy

Masahisa Koga, Kyosan Yoshikawa, Takayuki Obata, Jun-etsu Mizoe and Hiroo Ikehira

Keywords: magnetic resonance spectroscopy (MRS), positron emission tomography (PET).

Thirty seven patients with abnormal T2-elongated space showing a brain lesion in magnetic resonance imaging were studied with multi-slice proton magnetic resonance spectroscopic imaging (multi-slice 1H-MRSI) and positron emission tomography (PET). MRS images were obtained by combining volume-selective excitation with phase encoded acquisition. Choline maps were created and compared with PET maps of methionine metabolism. Choline signal elevation seen in brain neoplasms was associated with increased cellular proliferation. Elevation of choline signal seemed most cases of regrowth of brain tumor, whereas loss of choline signal showed brain necrosis (Figs. 28-30).
67. Synthesis and Preliminary Evaluation of \( ^{18}F \)FEtP4A, a Promising PET Tracer for Mapping Acetylcholinesterase in vivo

Ming-Rong Zhang, Akio Tsuchiyama, Terushi Haradahira, Kenji Furutsuka, Yuichiro Yoshida, Takayo Kida, Junko Noguchi, Toshiaki Irie and Kazutoshi Suzuki

**Keywords:** acetylcholinesterase, Alzheimer's disease, \( ^{18}F \)FEtBr, \( ^{18}F \)FEtP4A, Positron emission tomograph (PET) tracer

Postmortem studies on patients with Alzheimer's disease showed a reduction in the activity of acetylcholinesterase (AchE) in the neocortex and hippocampus, compared with normal subjects. To measure brain AchE activity and further elucidate the relationship between AchE and Alzheimer's disease, \( ^{18}F \)-18-fluoroethyl-4-piperidyl acetate (\( ^{18}F \)FEtP4A), a F-18 analog of \( ^{12}C \)-MP4A, was designed, synthesized and evaluated as a PET tracer for imaging AchE in vivo.

Since this tracer, possessing aminooalkyl acetate moiety, is an acetylcholine derivative, \( ^{18}F \)FEtP4A may readily enter the brain and be specifically metabolized by AchE into the hydroxy product (\( ^{18}F \)FEtP4OH) which can be retained at the site of the hydrolysis enzyme in the brain. Moreover, the longer half-life of \( ^{18}F \) offers the advantage to get more precise AchE activity information in the PET measurement, and to deliver the tracer to other facilities. Based on these considerations, \( ^{18}F \)FEtP4A is expected to become a useful PET tracer for measurement of AchE activity in vivo.

\( ^{18}F \)FEtP4A was prepared by reacting 4-piperidyl acetate (P4A) with 2-\( ^{18}F \)fluoroethyl bromide (\( ^{18}F \)FEtBr) using a newly developed automated system with 76±4 min of total synthesis time from the end of
bombardment. At the end of the synthesis (EOS), 380 ±120 MBq (n = 3) of $[^{19}F]$FETP4A were obtained after 15-25 min proton bombardment at a beam current of 15 μA with 49 ± 18% of radiochemical yield (based on $[^{19}F]$FETBr, corrected for decay). The radiochemical purity and specific activity of $[^{19}F]$FETP4A were 97 ±1.9% and 270 ± 45 GBq/μmol at EOS. In the final product solution (10 mL), the contamination of P4A was quantified using LC/MS and determined to be 0.06-0.2 ppm. Preliminary evaluation showed that the initial uptake of $[^{19}F]$FETP4A into mouse brain was > 8% injected dose/g tissue. The radioactivity washout of $[^{19}F]$FETP4A from all regions examined on the stationary phase (10-120 min after iv injection) followed monoexponential curves with similar elimination rates with half-lives of about 30 min. The rank of uptake of $[^{19}F]$FETP4A in these regions on the stationary phase agreed with that of AChE in the brain: striatum > cerebral cortex > cerebellum. The chemical analysis of in vivo radioactive metabolites indicated 83% of $[^{19}F]$FETP4A was hydrolyzed to $[^{19}F]$FETP4OH at 1 min postinjection, suggesting that this hydrolysis process was mediated by AChE. Therefore, this tracer may be useful as an imaging agent for mapping the AChE activity in vivo and assessing the extent of cholineric neuronal damage in Alzheimer's disease.

Publications:

68. Effect of Donepezil on Brain AChE Activity in Patients with Alzheimer's Disease Measured by PET

Hitoshi Shinotoh, Kiyoshi Fukushima, Shin-Ichiro Nagatsuka, Hiroki Namba, Akiyo Aotsuka, Noriko Tanaka, Tsumeyoshi Ota, Shuji Tanada and Toshiki Irie

Keywords: positron emission tomography (PET), acetylcholinesterase, $[^{14}C]$-MP4A, Alzheimer's Disease, donepezil

Acetylcholinesterase (AChE) inhibitors such as donepezil have been used for the treatment of Alzheimer's disease (AD). The recent development of carbon-11 labeled acetylcholine analogues such as $[^{11}C]$methylpiperoxidin-4-yl acetate ($[^{11}C]$MP4A) and propionate($[^{11}C]$MP4P) has made it possible to determine brain AChE activity by PET. We have measured the effect of donepezil on brain AChE activity in patients with AD. For the quantification of AChE activity, two methods of kinetic analysis were used: a standard non-linear least square (NLS) analysis using arterial input function and a simple method for direct estimation of AChE activity without the use of an arterial input function, namely "shape analysis".

Nine patients with probable AD (three men and six women, 60±7 years) participated in this study. Patients with AD were scanned once before and once during donepezil therapy (5 mg/day in 8 patients and 3mg/day in one patient). A sequence of 16 PET scans was acquired covering 60 minutes after intravenous injection of $[^{14}C]$MP4A (approximately 740 MBq) in each subject. Arterial blood samples were collected 24 times in 15 minutes after intravenous tracer injection for measurement of total radioactivity and metabolite analysis. A standard NLS analysis was performed to yield estimates of $K_t$ (transport into tissue), $k_t$ (tissue clearance of unchanged tracer into blood), and $k_s$ (hydrolysis rate of $[^{14}C]$MP4A by AChE, i.e. AChE activity) using metabolite corrected arterial plasma input function. In the shape analysis, $k_s$ values were estimated in the following formula: $C_{n}(t) - C_{n-1}(t) = k_s x C_{n-1}(t) x DT(t)$, where $C_{n}(t)$ is concentration of metabolic product at frame n, $C_{n-1}(t)$ is concentration of authentic tracer at frame n-1, and DT(n) is duration of the scan at frame n. The PET data consisting of observed (from 0 to 3min) and fitted (from 3 to 50min) data points were interpolated to yield an eight-fold increase in the number of data points prior to shape analysis calculation.

Authentic tracer was remarkably increased by factors of 1.5 at the peak and 3.5 at 15 minutes after tracer injection during donepezil therapy compared with the baseline study. In the NLS analysis, $k_s$ values in the cerebral cortex were 0.061±0.004 min⁻¹ (mean±SD, n=9) in the baseline study and 0.038±0.005 min⁻¹ (n=9) during donepezil therapy. The % inhibition of cortical $k_s$ values by donepezil therapy was 37.5±7.1% (n=9) in the NLLS analysis. In the shape analysis, cortical $k_s$ values were 0.056±0.006 min⁻¹ (n=9) in the baseline study and 0.039±0.005 min⁻¹ (n=9) during donepezil therapy. The % inhibition of $k_s$ by donepezil therapy was 30.3±4.4% (n=9) in the shape analysis. In both methods, cortical $k_s$ values were highly significantly reduced by donepezil (n=9, p<0.0001 in paired t-test). There was a trend toward linear correlation between % inhibition in the NLLS analysis and the shape analysis.

The present results suggest the feasibility of measuring the effect of clinical doses of donepezil by PET for both methods of kinetic analysis with $[^{14}C]$MP4A. These techniques may be useful for...
monitoring therapeutic effect of AChE inhibitors in AD.

Publication:


Shin-ichiro Nagatsu, Kiyoshi Fukushi, Hitoshi Shinotoh, Noriko Tanaka, Akiyo Aotsuka, Tsuneoishi Ota, Hiroki Namba, Shuji Tanada and Toshiaki Irie

Keywords: positron emission tomography (PET), acetylcholinesterase, [11C]-MP4A, kinetic analysis

N-[11C]Methylpiperidin-4-yl acetate ([11C]MP4A) has been used for positron emission tomography (PET) to determine cerebral regional acetylcholinesterase (AChE) activity quantitatively. The arterial input function is required in the conventional kinetic analysis of [11C]MP4A PET data using nonlinear least squares optimization. We have evaluated a simplified kinetic analysis based on a reference tissue without using an arterial input function.

The kinetics of irreversible radiotracers has been analyzed by a linear algorithm involving tissue radioactivity C(t), arterial input function Ca(t), and kinetic parameters of K.(transport into tissue), k.(tissue clearance of tracer into blood) and k.(irreversible transfer rate):

\[ C(t) = K_1 \int Ca(t) dt + K_1 k_1 \int C(t) dt - (k_2 + k_3) \int C(t) dt \]

Because [11C]MP4A showed flow-dependent kinetics in regions with very high AChE activity such as striatum or cerebellum, we assumed that the time-courses of radioactivity in these reference tissues were equivalent to the integral of arterial input function, and derived the following operational function:

\[ C(t) = K_r C_r(t) + K_r k_3 \int C_r(t) dt - (k_2 + k_3) \int C(t) dt \]

where C_r(t) is radioactivity of reference tissue and K_r is the ratio of K_r between target and reference tissues.

[11C]MP4A PET data obtained from 10 normal subjects and 20 patients with Alzheimer's disease (AD) were analyzed by the linear least squares analysis (LLS) using a reference tissue and the nonlinear least squares analysis (NLS) using the arterial input function to obtain regional k_1, an index of AChE activity. When the cerebellum was used as the reference tissue, LLS gave an almost identical neocortical k_1 as NLS ([LLS k_1] = 0.99[NLS k_1], r = 0.95, p < 0.001). Meanwhile, LLS using the striatum was susceptible to head motion of subjects because of smaller ROI size. Reduced neocortical AChE activity in AD patients as compared with normal subjects was shown by LLS of 21.4% (average of 5 regions), which was also comparable with the result from NLS (24.3%). Additionally a Monte-Carlo simulation study showed both LLS and NLS gave stable k_1 estimates (bias within ±5%, CV less than 10%) for regions with k_1/k: ratio of up to 2.0, covering the regions with low (cortex) to moderate (thalamus) AChE activity.

The present LLS using a reference tissue was almost equivalent to NLS in determining regional AChE activity in cortex and thalamus. We conclude that this non-invasive method is practical and useful for quantitative measurement of cortical AChE activity with [11C]MP4A.

Publication:

70. Brain N-acetylaspartate Is Elevated in Pelizaeus-Merzbacher Disease with PLP1 Duplication

Jun-ichi Takanashi, Mika Tomita, Hiroo Ikehira, Shuji Tanada, Eiji Yoshitome and Youichi Kohno

Keywords: Pelizaeus-Merzbacher disease, proteolipid protein gene 1, proton MRS

We assessed alterations in brain metabolites of patients with Pelizaeus-Merzbacher disease (PMD) with the proteolipid protein gene 1 (PLP1) duplications using quantitative proton MRS. Five unrelated male Japanese patients with PMD and PLP1 duplications were analyzed by an automated proton brain examination with the point resolved spectroscopy technique (repetition and echo time of 5,000 and 30 msec). Localized spectra in the posterior portion of the centrum semiovale were acquired, and absolute metabolite concentrations were calculated using the LCModel. Absolute concentrations of N-acetylaspartate (NAA), creatine (Cr), and myoinositol (MI) were increased by 16% (p < 0.01),
43% (p < 0.001), and 31% (p < 0.01) in patients with PMD as compared with age-matched controls. There was no statistical difference in choline concentration. The increased concentration of NAA, which could not be detected by previous relative quantitation methods, suggests two possibilities: axonal involvement secondary to dysmyelination, or increased cell population of oligodendrocyte progenitors. Elevated Cr and MI concentrations may reflect reactive astrocytic gliosis. Our study thus emphasizes the importance of absolute quantitation of metabolites to investigate the disease mechanism of the dysmyelinating disorders of the central nervous system.

Publication:

71. The Measurement of the Electrical Properties of Human Skin and the Variation among Subjects with Certain Skin Conditions

Takahiro Sunaga, Hiroo Ikehira, Shigeo Furukawa, Hiroshi Shinkai, Eiji Yoshitome, Takayuki Obata, Shuji Tanada, Hajime Murata and Yasuhiro Sasaki

Keywords: dielectric constant, human skin, skin conditions, MRI

In this study the dielectric properties are reported for human skin tissues over the frequency range 1-450MHz at 36°C. Healthy volunteers, collagen disease patients and dialysis patients are studied in order to investigate, primarily, the variability among (1) different regions of one individual, (2) the same region among different individuals and (3) skin conditions due to diseases. Considerable differences exist among skin dielectric properties obtained from different regions of one individual body. Although region dependence is observed, larger variability is found even in the same skin region among individuals.

The results indicate that considerable differences exist between the skin dielectric properties obtained from different regions of one individual body. These wide range distributions reflect variations in tissue composition. Biological tissues are inhomogeneous and have considerable variability in structure and composition and hence in dielectric properties. In addition, differences between subjects are also revealed. The variability of mean values at higher frequencies is 20, 5, 8 and 3% in palm, temple, neck, and abdomen regions, respectively.

Although results from some regions such as the abdomen agree, it is found that dielectric constant values of the same regions can have a difference of more than 20% over the entire range of frequencies between two subjects. Conductivity values are obtained from the expression \( \sigma = 2\pi f \varepsilon_0 \xi_\sigma \), where \( \xi_\sigma \) is the loss factor of complex permittivity, \( \xi_\sigma \) is the dielectric constant of free space and \( f \) is the frequency of the applied electromagnetic field. The experimental data points shown at each frequency are the average set of three to five measurements on this region of each subject, and in all cases the inaccuracy of measurement is never greater than 5%. This inaccuracy can be attributed to a combination of experimental error and the natural heterogeneity of the tissue. Measurement on distilled water produces both relative dielectric constant and conductivity values within 1.5% of the literature values at the lower frequencies and more accurate values (less than 1%) at higher frequencies. Thus, this decreased accuracy has evidently arisen from heterogeneity in the skin tissue rather than from experimental errors. The spectrum of the relative dielectric constant \( \xi_\sigma \) displays a high frequency tail and frequency dependence decreases generally as \( \xi_\sigma \) dispersion up to about 200 MHz. At frequencies above around 200 MHz, the value of \( \xi_\sigma \) decreases very slightly with frequency while the conductivity \( \sigma \) increases gradually. The total spreads from the mean values among the five subjects are estimated to be about 19% and 12% in the dielectric constant and 27% and 24% in conductivity values at 64 MHz and 420 MHz, respectively.

No remarkable change is detected in the dielectric constant among the three groups. Region dependence of dielectric properties is observed. The spreads at lower frequency on the tail of dispersion are larger than at higher frequency. This tendency is generally observed in both dielectric constant and conductivity.

From our study and other previous reports, it is acknowledged that most of the relative dielectric constant values of the human skin are distributed in the range 20-50, while the conductivity values are in the range 0.1-0.8 at frequencies higher than 200 MHz.

Publication:
72. Decreased Dopamine D2 Receptor Binding in the Anterior Cingulate Cortex in Schizophrenia

Tetsuya Suhara, Yoshiro Okubo, Fumihiko Yasuno, Yasuhiko Sudo, Makoto Inoue, Tetsuya Ichimiya, Yoshifumi Nakashima, Kazuhiro Nakayama, Shuji Tanada, Kazutoshi Suzuki, Christer Halldén and Lars Farde

**Keywords:** schizophrenia, positron emission tomography (PET)

The clinical efficacy of dopamine D2 receptor antagonism on the psychotic symptoms of schizophrenia has been widely demonstrated. However, most in vivo imaging studies have not been able to detect significant changes in striatal D2 receptors in schizophrenia. On the other hand, a number of studies have reported abnormalities in the cerebral cortex of schizophrenia. The aim of this study was to examine the extrastriatal D2 receptors of patients with schizophrenia.

Eleven drug-naive male patients with schizophrenia were examined with positron emission tomography using $[^{18}C]$FLB 457. Symptoms were assessed using the brief psychiatric rating scale (BPRS). Eighteen healthy controls were used for comparison. Region of interest analysis was performed using the reference tissue method and binding potential (BP) was used for the index of dopamine D2 receptor binding. The BP value was significantly lower, by about 12.5 %, in the anterior cingulate cortex in drug-naive patients with schizophrenia than in normal controls. A significant negative correlation was observed between BP in the anterior cingulate cortex and the positive symptom score on BPRS. It was concluded that lower BP values indicate fewer D2 receptors in the anterior cingulate cortex in patients with schizophrenia. Alterations in D2 receptor function in the extrastriatal region may underlie the positive symptoms of schizophrenia.

73. Development of an ECR Ion Source for Carbon Ion Therapy

Masayuki Muramatsu, Atsushi Kitagawa, Yukio Sato and Satoru Yamada

**Keywords:** ECR, carbon ion therapy, ion source

Ion sources for medical facilities should have characteristics of easy maintenance, low electric power, good stability and long lifetime (on the order of one year). A compact ECR ion source with all permanent magnets is one of the best types for these purposes.

A tentative goal of the source performance has been set at around those of existing 10 GHz NIRS-ECR ion source. The size of the magnets and their arrangement were determined in a way that both the peak and minimum values in the mirror field become close to those of the 10 GHz ion source. The magnetic field was calculated using the POISSON/SUPERFISH code. We measured the magnetic field to confirm the difference between the calculated and measured values by using a Hall generator. The results showed a small reduction compared to the designed value; 10% in the maximum mirror field and 5% in the sextupole field, though these reductions should be acceptable.

Based on previous experience with the ECR ion source, we modified the structure for the present source regarding three points. First, the length of the sextupole magnet was extended to cover the full mirror field region, aiming at good confinement of electrons. Second, the extraction electrode was cooled by water. This modification was very effective to reduce outgassing from the chamber wall and to keep a good vacuum around the extraction region, even for cw operation. Third, the Einzel lens was moved 150 mm away from the ion source, which enabled us to suppress the PIG discharge due presumably to the leakage of magnetic flux. These modifications raised reliability of the source. A schematic view of the modified source is shown in Fig. 31.

Tuning parameters of the source are only three; gas-flow rate, microwave power and frequency, which ensure easy operation. The microwave frequency is changeable between 9 and 18 GHz, with the maximum power of 300 W. A traveling-wave-tube (TWT) amplifier was employed in order to find the optimum frequency for the fixed and uncontrollable magnetic field.

The ion source has been operated both under pulse and cw modes with the TWT amplifier. In the case of low-duty pulsed mode operation (2 Hz, 3.5 ms), the source can produce the intensity of 180 $\text{eA}$ for C$^+$, which is close to our goal of 200 $\text{eA}$. In this case, the microwave frequency is 10.524 GHz, the microwave power is 300 W and the extraction voltage is 25 kV. Our best record for C$^+$ is 220 $\text{eA}$. In the case of high-duty pulsed mode operation (300 Hz, 1 ms), the beam intensity of 100 $\text{eA}$ is obtained for C$^+$ with good stability. Our best record under this mode is 140 $\text{eA}$, which is somewhat smaller than the required value. The poor intensity under the high-duty mode seems to be due to outgassing from the heated plasma chamber; the yield of highly charged ions generally decreases as the vacuum becomes worse.

The emittance is one of the most important information to judge beam qualities. The horizontal
emittance of $C^{+}$ ions with CH$_{4}$ gas was measured using a multi-slit and a scanner. The multi-slit has 13 slits with a spacing of 6 mm and a width of 0.4 mm. The scanner is located 80 mm downstream from the multi-slit. Parameters of the source are optimized to the production of $C^{+}$ and the beam intensity is 140 $\mu$A in cw operation. The 90% emittance of $C^{+}$ is $240 \pi$ mm mrad (unnormalized), which is 3 times larger than the expected value ($80 \pi$ mm mrad). We believe that this is due to non-optimization of the extraction scheme.

In the case of the high-duty pulsed mode, the beam intensity of 140 $\mu$A for $C^{+}$ is obtained which does not reach the required value (200 $\mu$A). The ion source will, therefore, be systematically tested by using a double-frequency heating technique and a biased disk method in order to increase the beam intensity. The horizontal emittance is quite large ($240 \pi$ mm mrad). In order to improve this, optimization of the extraction configuration will also be necessary.

Publications:

74. Evaluation of Functional Changes in the Cerebral Cortex with Clustering: Multi-functional PET Images Taken Pre- and Post Operation

Hinako Toyama, Kazuhiro Takazawa, Tadashi Nariai, Koji Uemura, Kenji Ishii, Keiichi Oda and Michio Sendai
(‘Waseda Univ.; ’Tokyo Medical and Dental Univ.; ’Tokyo Metropolitan Institute of Gerontology)

Keywords: positron emission tomography(PET), hemodynamic deficiency

We developed a method of clustering the brain pixels on the basis of different stages of hemodynamic deficiency using three sets of PET images and applied it to evaluate the regional vasodilative and vasoconstrictive reactivity before and after revascularized surgery in chronic occlusive cerebrovascular disease.(Fig.32). The 3D brain surface, representing the cortical rim in the transaxial images, was projected on a 2D plane by utilizing a Mollweide projection because of the advantages of treating the cortical rim once and saving computation time. Four anatomically and pathophysiologically different areas were delineated with four clusters in these two cases with cerebrovascular disease. (Figs.33-35). Functional changes in the revascularized region are depicted on the clustered brain images.
Fig. 32. Three-variable correlation map, in which the pixel values of resting CBF, the hyperventilatory (HV) response, and the acetazolamide (AZ) response was plotted on X-, Y-, and Z-coordinates, respectively. The clustered correlation maps of three variables by means of agglomerative hierarchical method (left-lower).

Fig. 33. Two cases with ICA occlusion (case 1 and case 2) were analyzed together by using a correlation map. **Case 1**: A 60-year-old male with occlusion of the right cervical ICA. The territories of the right anterior cerebral artery (ACA) and middle cerebral artery (MCA) were only fed by a poorly developed anterior communicating artery from the left side. Since the right posterior cerebral artery (PCA) was not visualized by vertebral angiography, the occluded right ICA was thought to have had a fetal-type posterior communicating artery. The patient once presented transient left side weakness and was found to have multiple cerebral infarctions on MRI. The superficial temporal artery (STA)-MCA anastomosis was performed on the right side. PET studies were performed before and three and eleven months after the surgery. **Case 2**: A 53 year old male with severe (> 95%) stenosis of bilateral cervical internal carotid and bilateral intracranial vertebral artery. He presented transient weakness on right extremities and small infarction was detected on left parietal subcortical area. Staged cervical endarterectomy was performed at first on the right side and hal year later on the left side. Before, during and after the operation, he did not present any ischchemic symptom again. PET measurement was performed before the operation, 2 months after the first and the second operations.
Fig. 34. (Case 1: ICA occlusion) The upper row shows 2D-projection images of pre- and post-operative CBF, HV, AZ and clustered maps. The mean and SD values are shown in the middle row; #4 (red) = cortex with hyper CBF and hyper responses to AZ and to HV, #3 (yellow)= normal, #2(green)= cortex with impaired vasodilative response to AZ and less vasoconstrictive response to HV and #1 (blue) = cortex with abnormal value in all three variables. In the patient with the occlusion of ICA, the area of segment #1 located at the operated region in the pre-operative image became into segment #3 (normal) with revascularization in the post-operative (the STA-MCA anastomosis) image. The areas of each segment in three scans are shown on the right side of middle row. The % changes of area of each segment between two scans are shown in the lower row.
Fig. 35. (Case 2: ICA occlusion) The upper row shows 2D-projection images of pre- and post-operative CBF, HV, AZ and clustered maps. The mean and SD values are shown in the middle row; #4 (red) = cortex with hyper CBF and hyper responses to AZ and to HV, #3 (yellow) = normal, #2 (green) = cortex with impaired vasodilative response to AZ and less vasoconstrictive response to HV and #1 (blue) = cortex with abnormal value in all three variables.
This clustering was considered to be useful for multivariate staging of hemodynamic deficiency in obstructive cerebrovascular disease and that it is suitable for objective representation of multiple PET parameters obtained in the activation study as well as in a study with $^3$O labeled CO$_2$, O$_2$, and CO gases. Two more cases involved Moyamoya disease (Fig. 36 and 37) and results with the method were satisfactory.

Fig. 36. (Case 3: Moyamoya disease) The upper row shows 2D-projection images of pre- and post-operative CBF, HV, AZ and clustered maps. The mean and SD values are shown in the left side of the lower; #4 (red) = normal cortex, #3 (yellow) = cortex with less vasoconstrictive response to HV and, #2(green) = cortex with impaired vasodilative response to AZ and less vasoconstrictive response to HV and #1 (blue) = cortex with abnormal value in all three variables. Case 3: A 40 year old male with moyamoya disease presented right hemianopsia and aphasia with left temporoparietal infarction. His aphasia recovered well but had been suffering from transient aphasia and right hemiparesis. Indirect bypass surgery (EDAS) was performed on bilateral side. His transient symptom completely disappeared after operation. PET measurement was performed before and one year after the operation.
Fig. 37. (Case 4: Moyamoya disease) The upper row shows 2D-projection images of pre- and post-operative CBF, HV, AZ and clustered maps. The mean and SD values are shown in the left side of the lower; #4 (red) = normal cortex, #3 (yellow) and #2(green) = cortex with normal vasoconstrictive response to HV and with impaired vasodilative response to AZ and #1 (blue) = cortex with abnormal value in all three variables. Case 4: A 14-year-old girl with occlusion of bilateral ICA (Moyamoya disease). The left MCA had poorer antegrade perfusion than the right MCA. The territories of bilateral MCA and ACA were also perfused from PCA through leptomeningeal collateral flow. The patient complained about transient weakness of left or right extremities. MRI showed no abnormality. The patient was treated by indirect bypass surgery (encephalo-duro-arterio-synangiosis, EDAS), in which the anterior and posterior branches of left STA, and the posterior branch of right STA were intracranially implanted. After the operation, she did not show transient weakness any more. Angiography one year after the operation demonstrated markedly improved collateral flow in the whole territory of the left anterior circulation through implanted vessels. It was demonstrated that the posterior part of the right anterior circulation was well fed by the external carotid artery. However, as the stage of the disease progressed during the follow-up period, the anterior part of right frontal lobe, where vessel was not surgically implanted, showed increasingly poor perfusion. An additional PET study was performed 14 months after the operation.

75. A Medical Image and the Database Archiving System at Research Center for Heavy Ion Therapy in NIRS

Hinako Toyama, Yoko Ikoma, Koji Uemura, Eiko Takeda and Shinnichirou Satou

Keywords: heavy ion therapy, DICOM, PACS, HIS, WEB viewer, relational database

To assess clinical trials of carbon ion therapy, an archiving system of medical images and clinical records for performed radiotherapy has been developed in our institute. The characteristics of this "A Medical Image and Database Archiving System (AMIDAS)" are:

1. to use WEB tools for the man-machine interface;
2. to connect organically to other systems such as HIS and the radiotherapy planning system in our hospital; and
3. to include data processing and statistical analyzing system.

Archiving all examined clinical data (images, biochemical data, pathological data and so on) and treatment history together make it possible to get information necessary to evaluate carbon ion therapy and related treatment for patients. This system consists of the image acquisition terminals connected into the imaging devices (CT, MR, PET), an image server, an image data backup device, a central information management system with database, a WEB server, a server for data analysis and image referring devices.(Fig.38). Basic personal information for a patient and results for a biochemical study which are registered and are managed at first in a hospital information system (HIS) are transferred into the central information management system in AMIDAS on the network.(Fig.39). Privacy of a patient is guarded with a security system such as a firewall and an access control system.

We show a clinical application of this system.(Fig.40).
Studies of SPECT, PET and CT were performed for a patient with lung cancer who received pre- and post-therapy with carbon ions. A method for co-registration among images of three modalities has been developed. Functional changes in perfusion, ventilation and V/Q ratio of the lung and especially around the tumor were evaluated. Relation between these functional changes and radiation dose was also studied by using the data in the server system. Changes in the tumor size and radiotracer accumulation after the radiotherapy were investigated by using CT and PET images. The data analysis is considered to offer a new concept for evaluation of tumor effect of the therapy.

The results of the clinical trial for a heavy ion therapy have to be distributed to other institutes in Japan and worldwide. Standardization of the database and the communication tool is desired. We are planning to extend our system while keeping it secure.
Fig. 39. Schema for the records in the database system System in NIRS

Fig. 40. A hospital information system connected to AMIDAS