Objectives

- To perform clinical research for clarifying usefulness of carbon ion therapy in order to establish new treatments for radioresistant tumors and to standardize the treatments for common cancers.
- To perform clinical research on utilization of the advanced technique of high-speed spot scanning irradiation of carbon ion beam in the routine treatment for head & neck or pelvic tumors.
- To investigate the benefits of improving accuracy of imaging modalities, such as PET, MRI, and CT scan for carbon ion therapy.
- To investigate the possibility of prediction or evaluation of effectiveness of carbon ion therapy using novel information from imaging modalities.
- To develop and regulate a comprehensive database on radiotherapy, mainly carbon ion therapy in consideration of achieving evidence-based medicine. Additionally, to propose a national database available for multi-institutional research on particle therapy carried out at domestic and foreign institutions.

Progress of Research

The Program of Research on the Standardization and Clarification of Charged Particle Therapy consists of the Clinical Trial Research Team, Applied PET Research Team, Applied MRI Research Team, and Clinical Database Research Team. All the teams are performing research and development on charged particle therapy. Progress of research in each team is summarized below.

1) Clinical Trial Research Team

As of March 2014, a total of 8,227 patients have been treated with carbon ion beams at our institute (Fig.1). Carbon ion radiotherapy of these patients was carried out as more than 60 different phase I/II or phase II clinical trials or advanced medicine.

Eight hundred and eighty-eight patients were treated as new patients from April 2013 to March 2014. This number is a new record for NIRS and about a 10% increase compared to the last year.

Fig. 2 summarizes the numbers of patients for each tumor site. Prostate, lung, head & neck, bone & soft tissue, and liver tumors are the leading 5 tumors in the trials and recently the number of pancreatic tumor patients has increased rapidly.

Scanning irradiation became available for the routine treatment of less mobile targets in the head & neck or pelvic region. More than 300 patients could be safely and efficiently treated with scanning irradiation at the New Treatment Research Facility.

Clinical trials for pancreas, esophagus, uterus, and kidney cancer are being conducted and patient enrollment has progressed. As an advancement of hypofractionated carbon ion therapy, the single session treatment for lung cancer and 12-fraction treatment for prostate cancer could be established and their applications as advanced medicine were started.

As a result of the clinical research done so far, it has been revealed that carbon ion radiotherapy provides a definite local control and offers a survival advantage without unacceptable morbidity in a variety of tumors that were hard to cure with other modalities. In addition, it was possible to implement hypofractionated radiotherapy using carbon ion beams, with application of larger doses per fraction and a reduction of overall treatment times as compared to conventional photon radiotherapy.

2) Applied PET Research Team

In the last year, this team completed modification of the PET respiratory gating system for detecting the respiratory signals at the end of the expiratory phase just as it is being achieved in the system of gated irradiation for heavy-ion radiotherapy. With this modification, it became possible to fuse the respiratory gating PET images with CT images for treatment planning taken in synchronization with the respiratory motion.

This year, some phantom experiments were done to confirm performance of the new respiratory gating system. Results of the
phantom experiments confirmed that the new respiratory gating system was able to detect the end of the expiratory phase and that the PET images obtained using this new respiratory gating system were better than those obtained using the conventional system.

3) Applied MRI Research Team

To provide quantitative diagnostic information for heavy charged particle therapy, several MR methods have been applied to clinical diagnosis. Advanced water diffusion monitoring in a tumor was performed using multi-level diffusion weighted MRI. The sequences for MR elastography were refined for world-wide delivery as a NIRS-made basic program (collaborative study with Siemens). MR and ultrasonic elastography in normal subjects were performed to obtain basic information for a combined clinical trial.

4) Clinical Database Research Team

It is strongly required to conduct multi-institutional clinical trials for standardizing carbon ion therapy in various tumor entities. Four running carbon therapy facilities in Japan, NIRS, HIBMC (Hyogo), GHMC (Gunma), and HIMAT (Saga) organized a cooperative study group to collaborate for this purpose. It is essential to prepare a dedicated database system to perform multi-institutional trials and to play a leading role in future trials. Thus, a database system was developed that can store integrated information on the patients treated at all the institutions of this study group. The data includes pretreatment information, treatment data, and outcome information. In addition, a conversion tool was developed that can unify the different ways of recording the medical information of each institution. For example, institution A uses “M” and institution B uses “0” to represent “male” on their database. The tool converts such differences of descriptions to the standardized description on our database.

References


Introduction
Alzheimer’s disease (AD) is characterized by formation of both senile plaques containing amyloid beta peptide (Aβ) derived from amyloid precursor protein (APP) and neurofibrillary tangles containing hyperphosphorylated tau protein (p-tau) in the brain that lead to progressive neuronal degeneration and death. Despite the fact that AD was identified more than 100 years ago, its cause remains elusive. There is mounting evidence, however, describing the effects of ionizing radiation (IR) on the brain, suggesting that exposure to IR is susceptible to ultimately favoring AD [1]. A recent study in mice reported early transcriptional response in the brain to low-dose (100 mGy) sparsely ionizing (low linear energy transfer (LET)) X-rays suggesting alterations of molecular networks and pathways associated with cognitive functions, advanced aging and AD. The possible cognitive and behavioral consequences induced by low-dose radiation are of great concern as humans are exposed to ionizing radiations from various sources including medical diagnosis. Although radiation therapy is an important tool in the treatment of primary and metastatic brain tumors, it is also responsible for various adverse neurological effects such as cognitive dysfunction and dementia. The present study was to investigate both the acute transcriptional alteration as well as the late pathological, cognitive and behavioral consequences induced by low-dose total body radiation (TBI).

Materials and Methods
Eight-week-old female mice of the C57BL/6J Jms strain were purchased from SLC, Inc. (Japan). The mice were maintained in a clean conventional animal facility under a 12-h light/12-h dark photoperiod. They were housed in autoclaved cages with sterilized wood chips and allowed free access to standard laboratory chow (MB-1, Funabashi Farm Co., Japan) and acidified water (pH = 3.0 ± 0.2) ad libitum. The mice were acclimatized to the laboratory conditions for 2 weeks as an adaptation period before use. As positive controls for detection of characteristic AD pathologies, two established AD mouse models were employed to ensure appropriateness of examination in the present study: transgenic Tg 2576 mice (Taconic Farms, Inc. USA) overexpressing human APP and PS19 mice overexpressing human tau. They were used as positive controls for detection of amyloid-related and tau-related pathologies, respectively. All experimental protocols involving mice were reviewed and approved by The Institutional Animal Care and Use Committee of NIRS. The experiments were performed in strict accordance with the NIRS Guidelines for the Care and Use of Laboratory Animals.

X-rays were generated with an X-ray machine (Pantak-320S, Shimadzu, Japan) operated at 200 kVp and 20 mA, using a 0.50-mm Al + 0.50-mm Cu filter. For high-LET heavy-ion irradiations, a monoenergetic ion beam of carbon particles was generated and accelerated by a synchrotron (a cyclic particle accelerator with its guiding magnetic field synchronized to the particle beam), the HIMAC, at NIRS. The beam energy was 290 MeV/nucleon corresponding to an average LET value of about 15 keV/μm. Ten-week-old C57BL/6J mice were total-body irradiated with an acute dose from X-rays (100 mGy) or carbon ions (50 or 100 mGy). The hippocampus was collected 4 hours and 1 year after irradiation and the expression of 84 AD-related genes was analyzed. Morris water maze test was applied to the measurement of the learning ability and memory of the animals. Amyloid imaging with PET was performed to detect the accumulation of fibrillary Aβ, and characteristic pathologies of AD were examined with immunohistochemical staining of APP, Aβ, tau, and p-tau. Statistical evaluation of the other data was carried out with the χ² test and Student t-test, as appropriate. Statistical significance was assigned to a value of P of <0.05.

Results
For the transcriptional studies on 84 AD-related genes after TBI, results (Table 1) on 100 mGy X-rays showed that only 1 gene was significantly down-regulated at 4 hours and two genes were down-regulated at 1 year; results on carbon ions showed that 3 genes
were markedly up-regulated at 4 hours after TBI with 50 mGy, 1 gene was up-regulated and 3 genes were down-regulated at 4 hours after TBI with 100 mGy, while only 1 gene was significantly down-regulated at 1 year after TBI with 100 mGy. On the other hand, for X-rays and carbon ions, PET imaging (Fig.1) and immunohistochemical staining showed no change in the accumulation of fibrillar amyloid and the expressions of APP, Aβ, tau, and phosphorylated tau were detectable in the animals 4 months and 2 years after TBI; the behavioral studies showed no significant difference on learning ability (Fig.2) and memory at 1 year and 2 years after irradiations [2, 3].

**Conclusion and Discussion**

This study complements previously reported work examining the acute transcriptional response of mouse brain to 100 mGy X-irradiations by providing further insight into the late consequences of both X-rays and carbon ions using a battery of examinations at transcriptional, behavioral and pathological levels. These findings suggest that TBI at a dose of 100 mGy could mainly induce early acute transcriptional alterations in some AD-related genes at 4 hours, and these transcriptional alterations did not appear to cause any significant changes regarding late impairment in spatial learning and memory at 1 and 2 years after irradiations, and did not seem to have any impact on induction of AD-like pathogenesis in the brains at 4 months and 2 years after irradiations. From a clinical point of view, these findings do not explore human health concerns that are generally implied following medical diagnostic exposure to IR and that exposure to low doses such as those found in the penumbra of the field are unlikely to result in AD. These findings indicate that radiation-induced changes in the expression of genes associated with AD are not necessarily predictors of the emergence of AD. The present work suggests that it is critical to perform more thorough studies on the late effects using such as pathological and behavioral parameters rather than just assuming that a change in gene expression means that AD would develop.

**Table 1** Transcriptional alteration in the expression of AD-related genes in hippocampi in mice after TBI

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Time after Irradiations</th>
<th>Dose</th>
<th>Gene</th>
<th>Transcriptional Alterations</th>
<th>Ratio to Control</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-rays</td>
<td>4 hours</td>
<td>100 mGy</td>
<td>Abp1</td>
<td>0.879 0.025 **</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 year</td>
<td>100 mGy</td>
<td>Lrp1</td>
<td>0.845 0.032 *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbon</td>
<td>4 hours</td>
<td>50 mGy</td>
<td>Abca1</td>
<td>1.222 0.011 *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 hours</td>
<td>100 mGy</td>
<td>Apoe</td>
<td>0.929 0.006 *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 year</td>
<td>100 mGy</td>
<td>L1α</td>
<td>0.932 0.024 *</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mice were exposed to TBI and the transcriptional alteration in the expression of AD-related genes in hippocampi was studied at 4 hours and 1 year after TBI. * P <0.05, ** P <0.01

**References**


After the TEPCO Fukushima Daiichi Nuclear Power Plant accident, all of the phone lines within NIRS were overwhelmed with inquiries from the general public, local government authorities, the media, etc. On 13 March 2011, NIRS researchers opened a dedicated telephone consultation line for the public (non-experts) in order to hear their various questions and worries about radiation exposure and to provide expert knowledge and evidence-based advice. This report is a tabulation of the contents of consultation calls made to the NIRS telephone consultation for the general public from 15 March 2011 to 31 March 2012. At present, this project is ongoing; this report is a collection of consultations from the year immediately following the accident. Readers may refer to the following site for details.


Consultants took notes during the phone consultations. Notes from 17,017 calls were amassed in the year following the accident. If data such as date/time of consultation, consultation length, attributes of the caller (gender, residence at the time of the accident and residence when calling) or details of the consultation topic were included in a note, only this information was transcribed and tabulated before the notes were disposed of.

Consultation topics were categorized as below.

- Exposure from the environment (12 topics)
  (e.g., air, rain, river, ocean, dirt, yard, hotspot)
- Radiation measurements and assessments (9 topics)
  (e.g., external / internal exposure, natural / accidental radiation)
- Decontamination and protection from exposure (9 topics)
  (e.g., evacuation, ventilation, agents, laundry, bathing)
- Food / water (4 topics)
- Various activities (3 topics)
  (e.g., hobbies / sports, agriculture, industry)
- Specific people (4 topics)
  (e.g., children, evacuees, patients)
- Other consultations (3 topics)
- Not consultations (6 topics)

The results are listed below:

(1) Over 5,000 consultations were received in the 17-day period in March 2011, but the number of consultations began to decrease in April (Fig.1). Mean time length per call in the year following the accident was 14.6 min.

(2) Female callers accounted for 60%-70% of the calls, and there was not much variation in gender proportions in the year after the disaster.

(3) Fig.2 shows ratios of consultations classified by residence area at the time of the accident. The percentage of the third category (Tokyo, Kanagawa, Yamanashi, Nagano and Niigata) showed decrease decreasing tendency.
(4) In the year from March 2011 to March 2012, the following four consultation topics were most common:

- Past exposure in areas outside the Fukushima power plants vicinity
- Children (pregnancy, childcare, school, etc.)
- Overall eating habits
- Consultations related to food and drink other than fish and water

(5) Time length of consultation for each consultation topic was tabulated. Those that were longer or shorter than the mean length (14.6 min) are listed in Table 1. For situations such as someone wanting to have an examination done or where answers were clear as to what was being asked, consultations tended to be shorter.

(6) Frequencies of consultations for changes in physical conditions for different residences at the time of the disaster were tabulated (Table 2). Although frequency decreased as the residence distance at the time of the accident from the Fukushima Daiichi Power Plant increased, the difference was small.

### Table 1 Consultation conversation lengths for each consultation topic

<table>
<thead>
<tr>
<th>Consultation topic</th>
<th>Mean (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparisons with atom bombs, Chernobyl</td>
<td>23.9</td>
</tr>
<tr>
<td>Contamination status of hotspots</td>
<td>20.8</td>
</tr>
<tr>
<td>Home decontamination methods</td>
<td>19.6</td>
</tr>
<tr>
<td>Demands/complaints for government, research institutes, etc.</td>
<td>19.0</td>
</tr>
<tr>
<td>Questions regarding radiation regulations and restrictions</td>
<td>18.3</td>
</tr>
<tr>
<td>Changes in physical condition</td>
<td>17.1</td>
</tr>
<tr>
<td>Mean length of all consultations</td>
<td>14.6</td>
</tr>
<tr>
<td>Want assessment of external exposure dose</td>
<td>12.2</td>
</tr>
<tr>
<td>Want an internal exposure examination</td>
<td>10.8</td>
</tr>
<tr>
<td>Want a different examination</td>
<td>9.3</td>
</tr>
</tbody>
</table>

### Table 2 Number of consultations about changes in physical conditions by residence at the time of the accident

<table>
<thead>
<tr>
<th>Residents at the time of the accident</th>
<th>(i) Fukushima</th>
<th>(ii) Iwate, Miyagi, Ibaraki, Tochigi, Gunma, Saitama, Chiba</th>
<th>(iii) Tokyo, Kanagawa, Yamanashi, Nagano, Niigata</th>
<th>(iv) Other areas or countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topics</td>
<td>6.0%</td>
<td>5.7%</td>
<td>5.0%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>
The needs for an imaging device that visualizes radioactive contamination have been considerably increased in Japan because of the Fukushima Daiichi Nuclear Power Station (FDNPS) accident in March 2011, which released large amounts of radioactive materials and contaminated the region around the FDNPS. Such an imaging device is expected to assist workers engaging in decontamination and nuclear reactor decommissioning tasks. If the distribution of radioactive contamination can be immediately and visually confirmed by an imaging device, the efficiency of decontamination work will be enhanced and the workers will be able to avoid unexpected exposure.

One of the candidates for the imaging device is a gamma camera (GC). It can visualize the distribution of radioactive contamination by detecting gamma-rays on the basis of a pinhole camera technique. Cs-137 is one of the most important radionuclides that contribute to the radiation dose rate in the region around the FDNPS and it emits gamma-rays with an energy of 662 keV (Fig.1); so the contamination by Cs-137 could be visualized by a GC.

In order to take an image of radioactive contamination by a GC, the GC has to measure each arrival direction of the gamma-rays from radiation sources to the GC, since to visualize something by gamma-rays is to know the gamma-ray flux variation dependent on arrival directions within the GC’s field of view. For that purpose, a GC consists of a two-dimensional (2D) sensor array and a thick lead container with a pinhole in front of the array (Fig.2a). The container works as a shield for gamma-rays and limits the arrival direction of the gamma-rays. Only gamma-rays that enter from the pinhole are detected. In this condition, the arrival direction of a gamma-ray can be uniquely determined as the direction along the line connecting the pinhole position to the point on the 2D sensor array where the gamma-ray is detected. A GC is based on this pinhole camera technique.

The disadvantage of GCs, however, is that their weight is typically around 20 kg and therefore too heavy for a person to carry around because of the thick lead container to shield gamma-rays from environment. It would be difficult to use a heavy GC for practical decontamination and nuclear reactor decommission tasks. Therefore, we decided to develop a new imaging device that is lightweight, low-cost and has high sensitivity.

We took note of the fact that Cs-137 emits not only gamma-rays but also characteristic X-rays with an energy of 32 keV (Fig.1) and decided to use X-ray detection instead of gamma-ray detection. The characteristic X-ray camera (CXRC) is also a kind of a pinhole camera but it is optimized to detect 32 keV X-rays from Cs-137 instead of 662 keV gamma-rays. The energy of the characteristic X-rays is about 20 times lower than that of gamma-rays and then it can be easily shielded by a thin stainless steel plate. As a result, the thickness and the weight of the CXRC container can be considerably reduced in comparison with that of a GC as illustrated in Fig.2b [1].

We have developed a prototype CXRC (Fig.3) that is based on the pinhole camera technique [2,3]. As a 2D X-ray sensor, an ar-
A ray of modules each of which consists of a CsI(Tl) scintillator coupled to a photomultiplier is employed. The 2D X-ray sensor array is fixed in a container made of thin metal. The weight of the prototype CXRC is 6.6 kg and the size is $225 \times 175 \times 242$ mm. The X-ray image measured by the CXRC can be superimposed on a visible image taken by a small camera installed on the front side of the CXRC.

To test the sensitivity of the CXRC, a standard source of Cs-137 with a radioactivity of 1 MBq was set on the floor of a laboratory at a distance of 1.3 m from the CXRC and it was visualized. As a reference for background level, we measured ambient dose equivalent rate with a survey meter and the dose rates with and without setting the Cs-137 source were 0.12 and 0.07 $\mu$Sv/h at the CXRC position, respectively. In other words, this test was made under the condition that the signal from the Cs-137 was almost comparable to the background. An image obtained by the CXRC is shown in Fig.4 when the CXRC was exposed for 5 s. We succeeded in visualizing the source within a very short time. The camera has sufficient sensitivity to find radioactive sources in a laboratory.

In order to apply this CXRC technique to the actual decontamination and nuclear reactor decommission tasks in the region around the FDNPS, we have continued to improve the performance of the CXRC. Another result of the measurement by the prototype CXRC when it was used to visualize a real contamination spot due to the FDNPS accident can be found in [3].

In addition, we have tried to reduce the weight of the CXRC prototype further. The weight of the prototype CXRC is currently determined by that of the container that includes the bulky photomultipliers. If the volume of the 2D sensor array is reduced, the weight of the CXRC will be considerably decreased and will be 1 to 2 kg. We expect that the 2D X-ray sensor array of CsI(Tl)s and photomultipliers can be replaced by semiconductors. We have finished fabricating an CXRC prototype that employs a semiconductor sensor array. Results obtained with this prototype will be presented in the near future.

References
Designation as WHO Collaborating Centre

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NIRS was designated as a World Health Organization Collaborating Centre (hereafter referred to as “WHO-CC”) on 2 September 2013. WHO-CC is a network consisting of highly regarded academic and scientific institutions worldwide designated by the WHO Director General that works together with WHO in order to implement its various programmes such as on nursing, occupational health, communicable diseases, nutrition, mental health, chronic diseases and health technologies utilizing its accumulated collective expertise. As of 2014, over 700 institutions in over 80 WHO Member States have been registered as WHO-CCs.

In accordance with the designation, NIRS cooperates with the WHO as its CC in the areas of: (1) strengthening preparedness for radiation emergencies and Radiation Emergency Medical Preparedness and Assistance Network (REMPAN) activities; (2) providing medical and technical assistance to WHO in response to and recovery after radiation emergencies; (3) carrying out biodosimetry and BioDoseNet (cytogenetics and internal contamination monitoring); (4) studying radiation protection for indoor radon; and (5) studying radioprotection in the field of medical exposure to ionizing radiation, with the focus on risks assessment and risk management.

The designation makes it possible for NIRS to further enhance contributions to national and international societies by leveraging its own large workforce, and its abundant research activities and accumulated experiences since its inception in 1957.

Radiation safety and radiation emergency medical preparedness are among the major research fields of NIRS. As the tertiary, the last bastion of, radiation emergency medical hospital in Japan, provision of medical treatment and response during accidents involving radioactive substances is also its important role. NIRS accepted three patients with high dose exposure from the JCO criticality accident in 1999. For the Tokyo Electric Power Company (TEPCO) Fukushima Daichi Nuclear Power Station accident, NIRS immediately dispatched experts to Fukushima on the early morning of 12 March 2011, and since then has taken initiatives in providing mitigation actions and supporting residents and workers in and around Fukushima Prefecture. In addition to emergency response, international workshops and training courses have been conducted by NIRS so as to foster medical profession-
basis (i.e., conducting capacity building assistance for national and international medical professionals and first responders who are involved in the emergencies, operating a 24/7 hotline on REM for medical personnel and emergency responders, cooperating with the central and local governments in order to establish a practical domestic system of REM, operating three network councils of REM, physical dosimetry, and cytogenetic dosimetry that offer an advisory and supporting framework complementary to the NIRS’s function). Furthermore, over 65 workers including medical doctors, nurses, experts on in-vivo and in-vitro dose assessment, radiation protection experts and administrators throughout the Institute are appointed as cooperative staff for REMAT. Should there be a request for REM assistance from WHO, REMAT is operated in the emergency response mode with both its original and cooperative staff members working together for WHO.

The study area of radiation protection for indoor radon is the other field included in the WHO-CC activities. Inhalation of radon gas (Rn-222 and Rn-220) and related radionuclides in the home and workplace is one of the main ionizing radiation risks causing deaths from lung cancer globally. In order to reduce this burden it is important that national authorities have methods and tools based on solid scientific evidence and sound public health policy. The NIRS is preparing to translate the *WHO Handbook on Indoor Radon* into Japanese; the handbook focuses on residential radon exposure from a public health viewpoint and provides detailed recommendations on reducing health risks from radon and sound policy options for preventing and mitigating radon exposure.

The area of radiation protection in the field of medical exposure to ionizing radiation with the focus on the risk assessment and risk management is the fifth field in the WHO-CC activities. NIRS organizes the Japanese Network for Research and Information on Medical Exposure (J-RIME), and has held meeting with experts, where a Japanese diagnostic reference level (DRL) for diagnostic modalities was discussed. NIRS also supervised translation of a booklet from the Royal College of Radiologists (RCR), *iRefer, making the best use of clinical radiology* into Japanese in order to raise awareness about medical exposure among Japanese radiologists. NIRS sent an expert to three meetings successively held in Geneva in September 2013, namely the “Radiation Risk Communication in Pediatric Imaging International Expert Meeting”, the “Global Initiative on Radiation Safety in Healthcare Settings, Focused expert meeting for project scoping - Medical imaging of asymptomatic people for individual health assessment -”, and the “Global Initiative on Radiation Safety in Health Care Settings, International Consultation”.

NIRS will continue to fulfill its functions in the above mentioned fields in cooperation with WHO.