Preface

It is my great pleasure to publish this Annual Report, which summarizes our major activities performed during the fiscal year 2007. The National Institute of Radiological Sciences (NIRS) was founded in 1957, and the year 2007 marked its 50th anniversary. During the past half century, we have continuously pursued our mission of conducting comprehensive research in science and technology related to radiation and human health, yet the final goal is still further ahead of us. In addition to the socio-economical activities, the increasing demand of energy consumption along with global warming of the earth requires new strategy for energy production and the natural environment of our planet. It is likely that our future society will heavily depend on nuclear power, and the appropriate handling of the risk and the benefit of radiation is urgently needed in our modern society. Dramatic increased use of radiological procedures in medical practice will be another important issue to be discussed. Based on our past experience and rich expertise, now is the time for us to work together in addressing these serious issues.

NIRS has a 50-years history of serving the community in promoting the safe and reliable use of radiation. We continue our work in collaboration with other institutions and with many scientific and technical experts who come to Chiba from all over the world. As facilities and human resources become limited through rising costs, collaboration and networking for cooperative projects present the only solution to realize our dream to be one of the international centers of excellence in radiological science. We sincerely ask for your strong support and advice as we work towards this goal.

Yoshiharu Yonekura, M.D., Ph.D.
President

1. Outline of Research Activities

The National Institute of Radiological Sciences (NIRS) was reformed in April 2001 as an Independent Administrative Institution, whose first Mid-term Plan (2001-2006) was successfully completed. In April 2006 the second Mid-term Plan was started. The research activities directly supported by the government were categorized and re-organized to five fields ; heavy charged particle therapy for cancer treatment, radiation effects on human bodies for use in radiotherapy, molecular imaging, radiation safety, and radiation emergency medicine. To perform these researches and related missions, four research centers and one fundamental technology center were established.

In this report, details of research activities performed during the 2nd fiscal year (April 2007 and March 2008) are described.

Judging from the number and quality of the presentations at scientific meetings as well as the research papers and reports, it can be concluded that the research activities are substantial and much progress has been achieved this year. The number of original papers published by the NIRS members reached 339 papers, and many of them were published in international journals with good reputations. Furthermore, we had more than 135 proceedings at international or domestic scientific meetings, 500 oral presentations, and 58 patent applications. Collaborative studies and exchanges of researchers were also very active : 94 collaborative studies were carried out, 1237 researchers worked as visiting stuff, and 420 students were accepted as trainees.

The clinical study of cancer treatment using the Heavy Ion Medical Accelerator (HIMAC), conducted in the Research Center for Charged Particle Therapy, was much progressed and more than 600 patients were treated this year. The total number of patients treated has reached more than 3800 since 1995. The development of new types of irradiation systems, such as spot-scanning system and rotating gantry has been progressed. The new irradiation facilities with these new systems will be completed at the end of this Mid-tem Plan (2011). Basic biological studies has been also conducted to demonstrate the biological effects of particle therapy and to develop further effective protocol for carbon ion therapy. In the Molecular Imaging Research Center, which was established in 2006, investigations on advanced imaging of cancer and neuronal function were carried out, mainly using positron emission tomography (PET) and MRI. Development of advanced measuring techniques including new types of PET probes was conducted with successful achievements. In this year, the Center also continued collaborating studies with other institutes and universities as a national center for molecular imaging under financial support of MEXT.

The research on radiation safety and emergency medicine, an important mission of the NIRS since establishment, were primarih carried out in the Research Center for Radiation Emergency the Research Center for Radiation Safety and Medicine. The research was focused on the health effects of low dose radiation, levels of natural radiation, radiation effects on environment (non-human biodata), and development of medical treatment and dose estimation at emergency. As a national hub center, the two centers also took place collaboration with international organizations including the International Atomic Energy Agency, International Commission of Radiation Protection, United Nations Scientific Committee on Atomic Radiation, World Health Organization, and so on.

The Fundamental Technology Center, which was newly established in this Mid-term to support various studies in the NIRS with advanced fundamental technology, carried out various developments including microbeam probes of cellular radiation response, neutron irradiation devices for animal experiments, and radiation measurement apparatus for cosmic rays.

Some other research programs were also continued or newly started with supports of funding agencies including the MEXT, the Ministry of Economy, Trade and Industry, the Ministry of Environment, and so on.

In the following pages, all the research activities carried out in the first year of the second Mid-term Plan are presented. I would like to express heartfelt thanks for cooperation and advice given to us during the FY 2007.

Hirohiko Tsujii, M.D., Ph.D.
Executive Director

2. Organization Chart and Budget

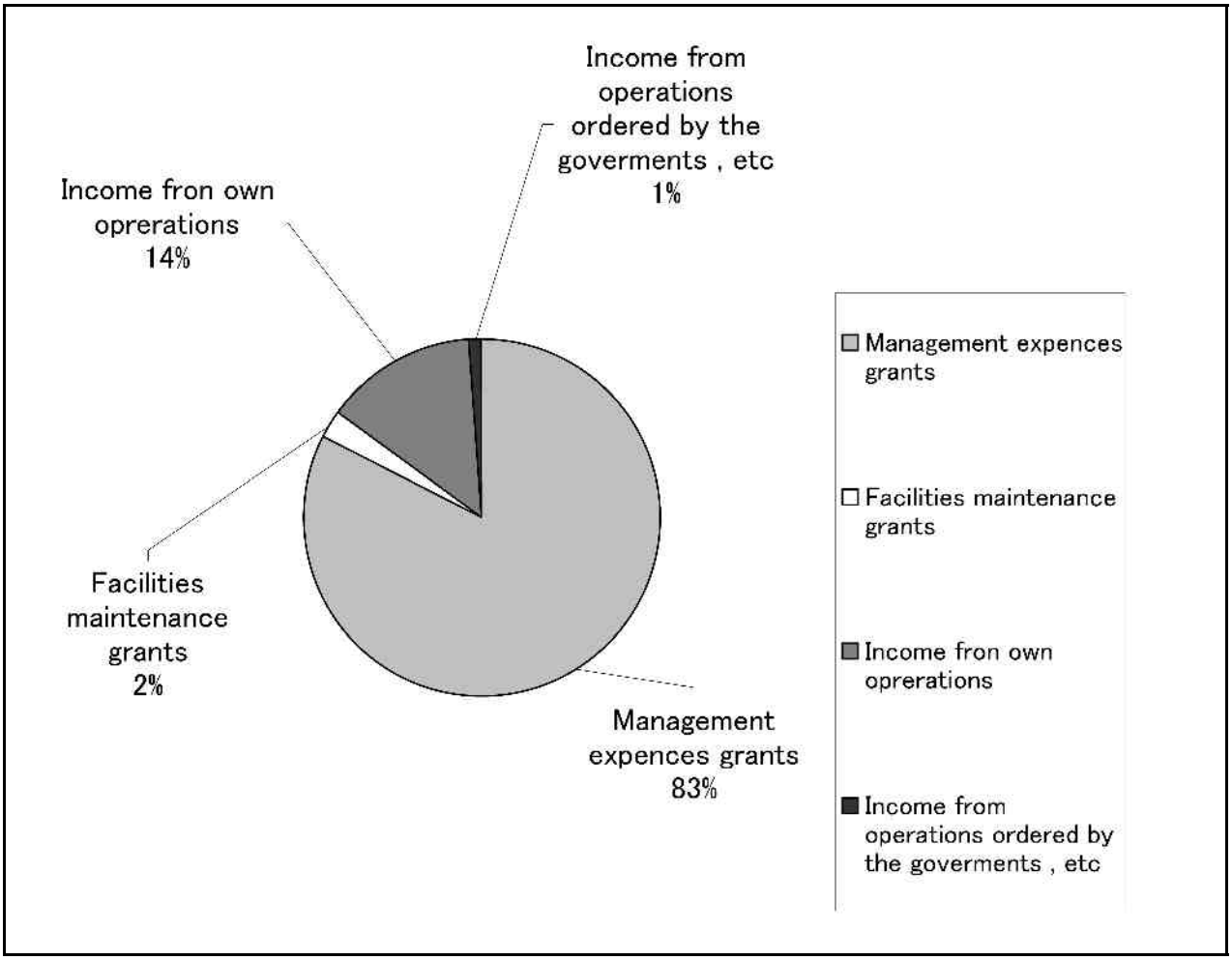
(1) Organization

Board of Executive Directors :
President
Executive Directors Auditors

- Department of Planning and Management
- Department of General Affairs
- Department of Information Technology
- Fundamental Technology Center
  - Planning and Promotion Office
  - Department of Technical Support and Development
  - Department of Safety and Facility Management
- Research Center for Charged Particle Therapy
  - Planning and Promotion Office
  - Hospital
  - Department of Accelerator and Medical Physics
  - Quality Control Section
  - Radiological Protection Section
  - Promotion of Carbon Therapy Section
  - Particle Therapy Research Group
  - Medical Physics Research Group
  - Diagnosis and Treatment Advancement Research Group
  - Radgenomics Research Group
  - Heavy-Ion Radiobiology Research Group
  - Transcriptome Research Group
- Molecular Imaging Center
  - Planning and Promotion Unit
  - Diagnostic Imaging Group
  - Molecular Neuroimaging Group
  - Molecular Probe Group
  - Biophysics Group
- Research Center for Radiation Protection
  - Planning and Promotion Office
  - Department of Advanced Technologies for Radiation Protection Research
  - Regulatory Sciences Research Group
  - Experimental Radiobiology for Children's Health Research Group
  - Radiation Effect Mechanisms Research Group
  - Environmental Radiation Effects Research Group
  - Nakaminato Laboratory for Marine Radioecology
- Research Center for Radiation Emergency Medicine
  - Planning and Promotion Unit
  - Department of Radiation Emergency Medicine
  - Department of Radiation Dosimetry
- Director of Special Research
- Audit Office
- Compliance Office

(2) Budget (2007.4～2008.3)

Total	15,555 million yen	%
Management expences grants	12,851 million yen	83%
Facilities maintenance grants	364 million yen	2%
Income fron own oprerations	2,147 million yen	14%
Income from operations ordered by the goverments , etc	193 million yen	1%



3. Research Center for Charged Particle Therapy

Hirohiko Tsujii, M.D., Ph.D.
Director, Research Center for Charged Particle Therapy

Outline of Research Career

Dr Tsujii received a Ph.D. from Hokkaido University in 1985 for his study on radiation therapy. He has been specializing in radiation oncology since 1969, and he has carried out work in particle beam therapy at New Mexico University, Tsukuba University and NIRS. He received the Princess Takamatsu Cancer Research Fund Scientific Award in 2005 and the National Institute of Science and Technology Policy NISTEP Award in 2006. He has been an honorary member of ESTRO since 2001 and a Coordinate Member, Science Council of Japan since 2006. He has been Director of the Research Center for Charged Particle Therapy, NIRS since 2003.

Objectives

The Research Center for Charged Particle Therapy (hereafter, abbreviated as "the Center") was established in 1993 when NIRS completed construction of HIMAC. Since then it has been carrying out clinical, biological and physics research using heavy ions generated from HIMAC. After accumulating clinical experiences with carbon ion radiotherapy in various types of malignant tumors, the Center was successful in obtaining approval from the Ministry of Health, Welfare and Labor for " Highly Advanced Medical Technology" in 2003. Thus carbon ion therapy has in the meantime achieved for itself a solid place in general practice. HIMAC has been also served as a multi-user utilization facility for medical, biological and physics studies for more than 500 researchers.

In 2006, when the second Mid-Term Plan of NIRS was initiated, the Center was reorganized to conduct life science research on ionizing radiation, focusing on carbon ion radiotherapy. Results obtained under this plan will eventually contribute to the improvement of the quality of human life. Research plans for the FY2007 include : clinical study on carbon ion radiotherapy for locally advanced tumors ; development and improvement of radiotherapeutic techniques ; design study and R&D for a new extension of the treatment rooms for HIMAC ; research on diagnostic imaging ; QA/QC for radiotherapy and radiation protection ; radiobiological experiments for improvement of radiotherapy ; exploration of variability of radiation sensitivity by investigating SNIPs ; the research on HiCEP.

Overview

The Center is organized into six research groups for two major topics (A and B) and one invited research project (C.) . Progress for each is summarized here.

1) Research on the use of heavy ion beams for cancer radiotherapy.

a) Development of advanced cancer radiotherapy with charged particle

This subject has been researched by the Particle Therapy Research Group (GL : T. Kamada) which consists of three teams : Clinical Trial Research Team, Clinical Database Research Team, and Radiation Effect Research Team.

From June 1994 to February 2008, a total of 3,819 patients were enrolled in nearly 50 different phase I/II and phase II trials and also in the project Highly Advanced Medical Technology of Carbon Ion Radiotherapy. In 2007, a total of 641 patients with a variety of malignant tumors were treated with carbon ions, among which nearly 75 % were in the technology project. Hypo-fractionated radiotherapy with employment of larger doses per fraction and shorter overall treatment time as compared to conventional photon radiotherapy has been effectively performed. The average number of fractions per patient reached 12 in 3 weeks. A new MLC (multi-leaf collimator) having fine leaves (2.5mm thick, 88 pairs) has been under development since 2005 and this year, we proved that its leakage dose was about 1% of the unshielded dose compared with the 0.6% leakage dose of the present MLC. This result was based on an estimation using the ratio of gap area of the new MLC to that of the present one. Of particular interest in the study was what particles contribute to the leakage dose. Protons were experimentally proved to be the biggest contributor and helium ions, the next biggest. Heavier particles contribute only slightly to the dose except for carbon particles. This experimental result was roughly reproduced by simulation done using the Phits code which was developed based on MCNP to simulate ion transportation.

For effective performance of charged particle therapy, a computer oriented information system is

mandatory. In 2007, we developed the IHE (Integrating the Healthcare Enterprise), EUA (Enterprise User Authentication) and PSA (Patient Synchronized Application) functions on the existing systems. These functions make it easy to operate multiple systems. Two PCs (for example : EMR and PACS-viewer) are commonly used for the Hospital Information System in one clinical unit. Many physicians have to enter a user ID and password to log into these systems. The developed functions of the IHE-ITI, EUA and PSA ease this troublesome manipulation. Middle-ware was developed for the EUA and PSA to reduce the implementation load among the EMR, PACS-viewer, report-viewer, radiation scheduling system and radiation information system.

Our group's study on the RBE model made remarkable progress this year. Biological response towards carbon ion beams as estimated with our current RBE model (NIRS model) was found to be almost equivalent to that by the microdosimetric kinetic model (MKM). MKM is in principle similar to the local effect model (LEM) used at GSI on the point that both are based on the superposition of a microscopic dose distribution and a cell. Survival curves of the mammalian cells in vitro for ^{3}He-, ^{12}C- and ^{20}Ne-ion beams were calculated by MKM and LEM. MKM reproduced well the survival curves while a modification should be introduced to LEM to reproduce the result. Comparison of the two models revealed that both require three basic constituents : target geometry, photon survival curve and track structure. In the context of the amorphous track structure model, the difference between the MKM and LEM was found to be primarily the result of different approaches calculating the biological effects of the extremely high local dose in the center of the ion track. At the end of the year, NIRS sponsored an international workshop on the issues of RBE of heavy ion beams. Prof. M. Scholz, the originator of LEM and Dr. R. Hawkins, the originator of MKM were invited together with other distinguished foreign scientists. The workshop contributed in deepening our understanding to the RBE modelling.

b) Development of a novel irradiation system for charged particle therapy

This subject has been researched out by the Medical Physics Research Group (GL : K. Noda) consisting of four teams : Accelerator Development Research Team, Irradiation System Research Team, Therapy System Research Team, and Compact Heavy Ion Therapy System Research Team.

Continuing on from the work in fiscal year 2006, research this year was focused on development of a 3-D scanning method with a pencil beam for the new treatment facility that was designed as an extension of HIMAC. This new facility is connected with the upper synchrotron at HIMAC. The underground treatment hall has three treatment rooms ; two are equipped with both horizontal and vertical beam-delivery systems and the third is equipped with a rotating gantry. Treatment-hall planning has been carried out in cooperation with medical staff in the HIMAC hospital. Two treatment-simulation rooms are also prepared for rehearsal of patient positioning and for X-ray CT observation of any change in the target size and shape during the whole treatment period. An additional six rooms are devoted to patient preparation before irradiation.

The extended flattop operation was successfully tested at the HIMAC synchrotron. In the raster-scanning experiment, using an extended flattop, the total irradiation time was considerably decreased to 20 s from 40 s under the routinely used operation period of 3.3 s. Further, the beam profiles during the extraction duration of 100 s were measured by a multi-wire proportional counter in the high-energy beam-transport line. From analysis of measurement results, it was estimated that both the position and the size for the 100s extraction were stabilized within (0.5 mm at the iso-center.

c) Standardization and improvement of therapeutic and diagnostic techniques

This research covers a wide range and has been performed by the Diagnosis and Treatment Advancement Research Group (GL : T. Kamada) consisting of four teams : Image Diagnosis Research Team, Image Processing Research Team, Quality Control Research Team, and Radiological Protection Research Team.

The Image Diagnosis Research Team has studied fundamental aspects in application of new PET tracers for oncology imaging. This year, tumor hypoxic imaging using ^{62}Cu-ATSM was initiated and bone metastasis imaging using ^{18}F- FNa was also investigated. For ^{62}Cu-ATSM, the team assessed the tracer distribution and carried out pharmacokinetic analysis in normal human volunteers in preparation for later application of the tracer to heavy ion radiotherapy patients. Activity of blood decreased relatively rapidly and reached its lowest level at about 10 minutes after injection. The liver and urinary system showed very intense activity in the Cu-62-ATSM whole body image. F-18-fluoride PET was shown to be more accurate than Tc-99m-methylene diphosphonate (MDP) bone scintigraphy for the detection of both sclerotic and lytic lesions in various malignancies.

The Image Processing Research Team analyzed organ movement during respiration using 4D CT (256MSCT) as applied to patients with lung carcinoma. Volumetric cine imaging of the lung satisfactorily

obtained continuous movement of the tumor in the sagittal section. The 256MSCT significantly improves the observation of tumor displacement and overcomes some of the limitations of present CT methods. Moreover, owing to its accurate determination of the margin, volumetric cine scan is a useful complement to current irradiation methods.

The Quality Control Research Team carried out comparative studies between glass dosimeters and TLD which had been used as a postal dosimeter. The results showed that the glass dosimeter features were appropriate for the postal dose audit. The team carried out a pilot study in which postal glass dosimeters were sent to hospitals in Japan. The study showed a 1.3 % standard deviation of dose among 100 responding hospitals. In November 2007, a regular dosimetry audit service for radiotherapy facilities was started using the glass dosimeter with a commercial base by the Association for Nuclear Technology in Medicine, in collaboration with National Cancer Center and NIRS.

The Radiological Protection Research Team has analyzed data for frequency and conditions in X-ray CT examinations performed last year, and started the next nationwide survey dealing with general X-ray examinations. There are more than 9,000 hospitals and about 100,000 clinics being targeted in the survey. Questionnaires have been made for survey and they cover patient information such as sex and age, and the equipment, frequencies, conditions etc. being used in the facilities.

2) Research on radiation effects for improvement of radiation therapy

a) RadGenomics research concerning the radiation sensitivity

This subject has been carried out by the RadGenomics Research Group (GL: T. Imai) consisting of three teams : Genetic Information Team, Molecular Radio-oncology Team, and Molecular Biostatistics Team.

Normal tissue reactions of cancer patients vary considerably after radiotherapy. A number of observations have indicated that certain genetic factors play important roles in this variability. The aim of the RadGenomics Research Group is to explore the genetic characteristics for both the patient and the bearing tumor, by which the potentially most effective radiotherapy can be delivered. From a molecular-biological standpoint, this will open the way to the development of an individual-oriented radiotherapy. Seven research studies were conducted: 1) haplotype-based analysis of genes associated with risk of adverse skin reactions after radiotherapy in breast cancer patients ; 2) radiation-induced cell-death signaling pathway activation by concurrent use of cisplatin in sequential biopsy specimens from patients with cervical cancer ; 3) chemoradiation-induced expression of fibroblast growth factor-2 and laminin in patients with cervical cancer ; 4) up-regulation of stress-response genes with cell cycle arrest induced by carbon ion irradiation in multiple murine tumors models; 5) visible haplotype-tag SNP typing array device for human radiation sensitivity-associated genes ; 6) gene expression analysis in human malignant melanoma cell lines exposed to carbon beams ; and 7) prediction of lymphatic metastasis based on gene expression profile analysis after brachytherapy for early-stage oral tongue carcinoma. These studies will contribute to identifying predictive markers for individual characteristics such as radiosensitivity for both malignant tumors and surrounding normal tissues.

Furthermore, the RadGenomics Research Group has established a collaborating network with five university hospitals and the Research Center for Charged Particle Therapy Hospital to allow for research "from bench to bedside".

b) Biological research concerning the improvement of radiation therapy

This subject has been carried out by the Heavy Ion Radiobiology Research Group (GL : R. Okayasu) consisting of four teams : Biophysics Team, Experimental Therapy Team, Cellular and Molecular Biology Team, and Radiation Modifier Team.

The geometric locations of ion traversals in mammalian cells constitute important information in the study of heavy ion-induced biological effects. The Biophysics Team has employed a contact microscopy technique which enables them to visualize cells on a plastic track detector and obtain positions of ion traversals. To investigate the relationship between LET and skin reaction, the Experimental Therapy Team has performed fractionated mono-peak irradiation on the normal mouse foot. The α/β ratios were 28 Gy^{-1}, 39 Gy^{-1}, and 38 Gy^{-1} at the LET values for 58, 13.6 keV/μm and γ rays, respectively. There seemed to be no significant difference among the α/β ratios.

The Cellular and Molecular Biology Team has demonstrated that cells irradiated with X-rays and heavy ion particles showed different radio-sensitivities depending on the DNA repair characteristics of the cells; in particular, homologous recombination (HRR) defective cells showed an extreme sensitivity to high LET heavy ion irradiation. This result suggested that these different ionizing radiations induced different types of DNA damage. The term is planning to further clarify the molecular mechanisms associated with heavy ion irradiation in order to support a successful clinical outcome.

The Radiation Modifier Team has studied three

subjects and obtained the following results. 1) In order to develop better compounds for free radical scavengers, several resveratrol analogs were synthesized and analyzed. The kinetic study of their in vitro free radical scavenging reaction showed that introduction of methyl groups on the phenyl rings of resveratrol increased the scavenging rate constant significantly. Introduction of three methyl groups resulted in the rate constant being more than 60 times larger than that of the original resveratrol. 2) The study of radioprotector, α-lipoic acid, was examined against the whole body Fe ion-irradiation (2.0 Gy). The cognitive dysfunction of mice caused by Fe ion-irradiation was ameliorated by the administration of α-lipoic acid before irradiation and oxidative stress to DNA, proteins, and lipids in the cerebellum caused by Fe ion-irradiation was also reduced by α-lipoic acid. 3) Redox- and oxygen-mapping was studied in a test using free radical reactions in a gelatin sample irradiated by heavy ion beams. Free radical reactions occurred in dose- and LET-dependent manners during carbon irradiation. The free radical yield obtained with heavy ion irradiation was expected to be less than 1/3 of that obtained with X-ray irradiation when the same dose for a deeper target organ was considered.

c) Transcriptome Research for Radiobiology

This research has been carried out by the Transcriptome Research Group (GL: M. Abe) consisting of 3 teams: Stem Cell Research Team, Gene Expression Profilling team, and Model Organism Research Team. The Stem Cell Research Team identified a new gene that expresses in both ES and spermatogonial stem cells (SSCs). The team generated its knockout mice and found a severe defect in mice spermatogenesis and an accumulation of SSCs in them. Further study revealed that the gene plays a role in the differentiation step of SSCs. In addition, the team is conducting a new project on iPS (induced pluripotent stem cell) to understand the molecular mechanism underlying their generation.

The Gene Expression Profiling Team attempted to improve the HiCEP method to allow analysis for even a small amount of starting materials. A new protocol was developed that uses less than 1 nanogram of total RNA, corresponded to less than 100 cells.

The Model Organism Research Team has been basically supporting other research teams, especially the stem cell research team. Gene KO mouse technology has been shown to be working. A transplantation test for testicular cells to assess their ability for spermatogenesis is now available. The team is attempting to introduce the technology for genome reprogramming using nuclear transfer.

3) Research Project with Heavy Ions at NIRS-HIMAC

On hundred twenty-four research proposals were accepted and carried out in FY2007 at HIMAC. The beam time of 5,679 hours was supplied to these proposals. Publications numbered 78 papers, 47 proceedings, while 309 papers were presented at various meetings. A total of 527 researchers, including 55 foreign researchers, participated in the project.

3.1. Developing Advanced Clinical Therapy with Charged Particles

Tadashi Kamada, M.D.,Ph.D.
Head, Hospital
Outline of Research Career

Dr. Kamada received a Ph.D. from Hokkaido University in 1996 for his study on radiotherapy of bile duct cancer. He has had 28 years of experience in clinical reseach on radiation oncology, including 13 years experience in carbon ion radiotherapy at NIRS. Since 2006, he has been group leader of the Particle Therapy Research Group for developing advanced clinical therapy with charged particles.

Contact Point : t_kamada@nirs. go. jp

Objectives

- Clinical studies to develop therapeutic techniques for diseases that are difficult to treat with other therapies (such as pancreatic cancer) and for which charged particle radiation therapy does not yet have a role.
- A study on optimizing irradiation methods by disease and by region, using clinical investigations of therapies in which radiation is combined with drugs and operations
- Development of a comprehensive database on treatment, clinical course and other factors. Comparison and analysis of domestic and foreign data on particle beam therapy.
- Annual treatment of 500 patients to maximize and disseminate the therapeutic effect of charged particle technology. This is the target number combining patients taking part in clinical studies and those receiving high-technology treatments, in consideration of the fact that the NIRS is primarily a research and development facility.
- Evaluation of the therapeutic effects of treatments developed by NIRS from the viewpoint of quality of life (QOL) and therapeutic costs. Patients' opinions are collected to gauge their level of satisfaction with the therapy.

Progress of Research

The Particle Therapy Research Group for developing advanced clinical therapy with charged particles consists of the Clinical Trial Research Team, Clinical Database Research Team, and Radiation Effect Research Team. It does research and development on charged particle therapy. Progress of research in each team is summarized below.

1) Clinical Trial Research Team

From June 1994 to February 2008, a total of 3819 patients were enrolled in clinical trials using carbon ion beams generated by HIMAC. Carbon ion radiotherapy of these patients was carried out by nearly 50 different phase I/II or phase II protocols and highly advanced medical technology. The Figure 1 lists the number of the patients for each tumor site treated with carbon ion beams.

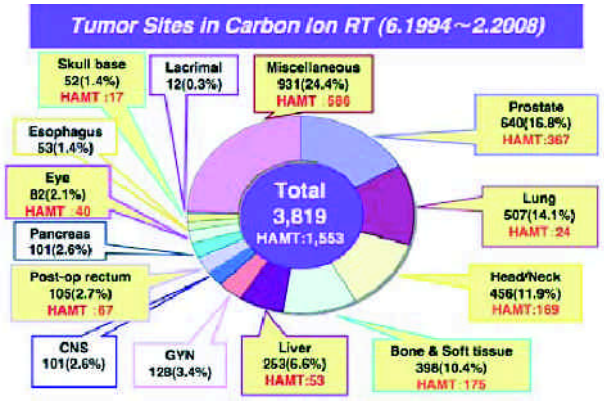


Fig. 1. The number of patients for each tumor site treated with carbon ion beams.

We treated 641new patients in FY2007. Prostate, lung, head and neck, bone and soft tissue, and liver tumors are the leading 5 tumor types in the trials. A total of 3178 patients who had a follow-up period of 6 months or more were included in this report. The clinical trial revealed that carbon ion radiotherapy provided definite local control and offered a survival advantage without unacceptable morbidity in a variety of tumors that were hard to cure with other modalities. Using carbon ion beams, it was possible to implement hypofractionated radiotherapy, with application of larger doses per fraction and a reduction of overall treatment times as compared to conventional photon radiotherapy. Carbon ion radiotherapy has been approved by the Ministry of Health, Labor and Welfare of Japan as "Highly Advanced Medical Technology

(HAMT) " since November 2003. Nearly 75 % of the patients receiving carbon ion radiotherapy were treated by HAMT in 2007.

When irradiating a patient with carbon beams, the patient should be protected from exposure to an unwanted dose. A multi-leaf collimator (MLC) and patient collimators are used to spatially limit the carbon beams for the sake of delivering high localization of the dose to a target. The MLC can easily form an arbitral aperture shape which conforms to a cross sectional shape of the target by computer control. However, since each leaf of the present MLC is 6.5 mm thick, it is difficult to make the fine shape which is required for the cases of cancers which are abutting critical organs, such as head and neck cancers. It these cases, a patient collimator is used, which is manufactured by boring an aperture in a brass block ; this takes a few days and is costly. Furthermore, use of the patient collimator has required radiation therapy technologists set the heavy collimator just above a patient in positioning. Omitting use of the patient collimator reduces the expense and the human burden.

A new MLC has been under development since 2005 which is applicable to the cases in which the patient collimator is usually required. The MLC is equipped with 88 pairs of a 2.5 mm thick leaf with 0.15 mm spacing. This thickness is almost 1/3 of the present thickness of 6.5 mm. Each leaf has a step-like structure, instead of a tongue-and-groove structure. We proved that the leakage dose of the new MLC was about 1% of the unshielded dose compared with that the 0.6% leakage dose of the present MLC. We estimated this by considering the ratio of gap area of the new MLC to that of the present one. Of particular interest in the study was what particles contribute to the leakage dose. Protons were experimentally proved to be the biggest contributor and helium ions, the next biggest. Heavier particles contribute only slightly to the dose slightly except for carbon particles. This experimental result was roughly reproduced by simulation done using the Phits code which was developed based on MCNP to simulate ion transportation. A more precise study by Monte Carlo simulation needs to be made.

2) Clinical Database Research Team

In October 2006, we implemented the Electronic Medical Record (EMR) and developed a simple input method for the patient's findings which include symptoms, tumor responses, and toxic reactions that should be estimated by the physician during the clinical interview. We improved the coordination among several database systems (Hospital Information System, Therapy Plan Database, Therapy Schedule Management System, two PACSs and Radiology Information System for Radiation Therapy). These systems are connected to each other and data are transmitted to the destination systems.

We also developed the IHE (Integrating the Healthcare Enterprise), EUA (Enterprise User Authentication) and PSA (Patient Synchronized Application) functions on the existing systems. These functions make it easy to operate multiple systems. Two PCs (for example : EMR and PACS viewer) are commonly used for the Hospital Information System in one clinical unit. Many physicians have to enter a user ID and password to log into these systems. The developed functions of the IHE-ITI, EUA and PSA ease this troublesome manipulation. We developed middle-ware for the EUA and PSA functions to reduce the implementation load among the EMR, PACS-viewer, report-viewer, radiation scheduling system and radiation information system. We realized that EUA and PSA functions were essential in a multi-system environment. Our middle-ware resolved the complexities of the application implementation. The established guideline was useful to unify the user interfaces of each application. We found that the EUA and PSA functions are critical for visual integration.

We implemented a system to share medical data between hospitals and medical institutions. This system is based upon the IHE Cross-Enterprise Document Sharing (XDS) which uses SOAP, ebXML RIM and Web Service Description Language (WSDL) and HL7. We prepared the Open Source Software license for the delivery of software. We are now developing the document source, document repository, document registry and document consumer that were defined by the IHE XDS. We are planning to make the software made available by autumn 2007. We think that it is very important to maintain this software and to improve the code periodically. We are working to establish a maintenance framework for the open source software.

We continued to promote standardization of the database, and the XML module for radiation therapy and to prepare ways to communicate clinical radiotherapy data with other hospitals and medical facilities. We analyzed the physician's workflow in radiation oncology departments of Japanese hospitals. In this workflow analysis, we classified the flow into four categories (initiation of radiation therapy, daily treatment, interruption and resumption, termination). These categories were suitable for Japanese environment.

The NIRS Hospital Information System was modified in 2006 and its status in January 2007 is shown in Fig. 2.

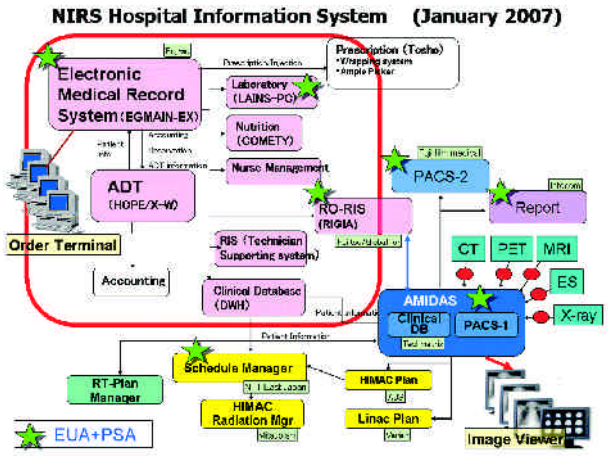


Fig. 2. Current status of Hospital Information System in NIRS.

3) Radiation Effect Research Team.

Based on the success of the retrospective TCP estimation in the case of NSCLC with a model by Webb and Nahum, in FY2007 we tried predictive estimation for the case of prostate cancer was tried in this year in order to determine starting dose in a hypo-fractionated study. In the case of prostate cancer, the main concern in determining prescribing dose is to avoid normal tissue complications rather than controlling the primal target (prostate) because the target has already been well controlled. GU is representative of the normal tissues to be considered when treating prostate cancer because it is inevitably included in the target area and suffers high dose irradiation. The dose response of GU toxicity under 20 fractions was analyzed with the model. The preliminary results showed a tendency to overestimate the isodose in 16 fractions. The model was revised in order to make it more applicable for the estimation of the normal tissue response. One of the difficulties in analyzing the response of normal tissues is that the number of incidences of a complication is quite rare and the result shows large statistic variation. From this viewpoint, the response of mouse skin has been studied for carbon ion beams with various energies and fractionations.

Our study on the RBE model made remarkable progress this year. Biological response against carbon ion beams estimated with our current RBE model (NIRS model) was found to be almost equivalent to that by the microdosimetric kinetic model (MKM). MKM is in principle similar to the local effect model (LEM) used at GSI on the point that both are based on the superposition of a microscopic dose distribution and a cell. Survival curves of the mammalian cells in vitro for ^{3}He, ^{12}C and ^{20}Neion beams were calculated by MKM and LEM. MKM well reproduced the survival curves while a modification should be introduced to LEM to reproduce the results. Comparison of the two models revealed that both require three basic constituents: target geometry, photon survival curve and track structure. In the context of the amorphous track structure model, the difference between the MKM and LEM was found to be primarily the result of different approaches calculating the biological effects of the extremely high local dose in the center of the ion track. At the end of the year, we sponsored an international workshop on the issues of RBE of heavy ion beams. Prof. M. Scholz, the originator of LEM and Dr. R. Hawkins, the originator of MKM were invited together with other foreign distinguished foreign scientists. The workshop contributed to deepening our understanding of the RBE modelling.

Major Publications

1) J. Mizoe, H. Tsujii, A. Hasegawa, T. Yanagi, R. Takagi, T. Kamada, H. Tsuji, et. al: Phase I/II clinical trial of carbon ion radiotherapy for malignant gliomas: combined X-ray radiotherapy, chemotherapy, and carbon ion radiotherapy., International Journal of Radiation Oncology Biology Physics, 69 (2), 390-396, 2007

2) D. Schulz Ertner, H. Tsujii: Particle Radiation Therapy Using Proton amd Heavier Ion Beams, Journal of Clinical Oncology, 25 (8), 953-964, 2007

3) S. Mori, M. Endo, S. Komatu, T. Yashiro, S. Kandatsu, M. Baba: Four-Dimensional Measurement of Lung Tumor Displacement Using 256-Multi-Slice CT-Scanner, Lung Cancer, 56 (1), 59-67, 2007

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3.2. Research on the Next-generation Irradiation System

Koji Noda, Ph.D., Director
Physics research Group

Outline of Research Career :

Dr. Noda received his B.S. degree from the Department of Nuclear Engineering, Kyushu University in 1979. After completing his M.S. program there in 1981, he worked on development of a PET cyclotron until 1989, and he concurrently studied accelerator physics from 1985 to 1989 in the Institute for Nuclear Study, University of Tokyo. In 1989, he joined the HIMAC project at NIRS, and he was engaged in construction and development of the HIMAC synchrotron. He received his PhD in 1992 from Kyushu University for the study of energy-loss cooling. Currently he is Head of Accelerator Development Section, and he holds the additional post of Director of the Medical Physics Research Group.

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Objectives :

Based on more than ten years of experience with HIMAC, we have proposed a new treatment facility toward adaptive cancer therapy with heavy ions, which makes the one-day treatment of lung cancer possible. Further, the new treatment facility should accurately treat a fixed target, a moving target with breathing and/or a target near a critical organ. To satisfy these purposes, the facility employs a 3D-scanning method with a pencil beam. We have proposed and studied a phase-controlled rescanning (PCR) method, especially for treating a moving target. A rotating gantry using the PCR method is also employed in order to reduce the patient's load, and to increase the treatment accuracy for a tumor near a critical organ through multi-field optimization. In addition, we have designed the beam-delivery system and the rotating gantry system and we have done the treatment flow including patient positioning and the facility planning. Related R&D work with HIMAC since 2006.

Progress of Research

1) Design study of new treatment facility

a) Energy and field size

A ^{12}C beam is used for treatments that have been carried out in the existing HIMAC treatment. The maximum ion energy is designed to be 430 MeV/n in both the horizontal and vertical beam-delivery systems, in order to obtain more than the residual range of 30 cm. The maximum lateral-field and SOBP sizes are 25 cm ×25 cm and 15 cm, respectively, in order to cover almost all treatments with HIMAC. On the other hand, the rotating gantry system employs the maximum energy of 400 MeV/n, the maximum lateral-field of 15 cm×15 cm and the maximum SOBP size of 15 cm, in order to downsize the gantry. Further, positron-emission beams, such as ^{11}C, will be used to verify the irradiation area and their ranges in a patient's body. This R&D work has been carried out in order to obtain positron-emission beams accelerated directly through the HIMAC accelerator, instead of using the projectile-fragmentation method.

b) Beam-delivery system

Both the horizontal and vertical beam-delivery systems consist of a pair of scanning magnets, dose monitors, a ridge filter and a range shifter. The total length of the beam-delivery system is around 9 m. The beam-scanning speed is designed to be 100 mm/ms for fast scanning. Two dose monitors, which are parallel-plate ionization chambers with an effective area of 250 mm^2, are used for dose management. The beam position and size are monitored by multi-wire proportional counters. Considering the slice thickness, the Bragg peak is slightly spread out by a mini ridge filter. The range shifter is utilized to change the slice in the target. Thus, the range shifter should be as close as possible to the iso-center in order to avoid any change of the beam size by multiple scattering through the range shifter. In the present design, the rotating gantry employs a pencil-beam raster scanning, which is identical to the scanning used for the horizontal and vertical beam-delivery systems. It is important for the gantry design to avoid any change of the beam size dependence on the rotation angle. Thus, we will adapt a compensation method for the asymmetric phase-space distribution. This method is based on multiple scattering by a thin foil placed at the position with the optimum beam-optical parameters in the beam-transport line. Further, the final dipole magnet is divided into 30-degree and 60-degree magnets, and two scanners are placed between the two dipole magnets in order to extend the effective length from the scanners to the iso-center. The total weight of the gantry system is around 350 tons.

c) Facility planning

The new treatment facility is connected with the upper synchrotron at HIMAC. The underground treatment hall has three treatment rooms in order to treat around 1000 patients per year. Two rooms are equipped with both horizontal and vertical beam-delivery systems, and the third is equipped with a rotating gantry. Treatment-hall planning has been carried out in cooperation with medical staff in the HIMAC hospital. Two treatment-simulation rooms are also prepared for rehearsal of patient positioning and for an X-ray CT observation of any change in the target size and shape during the whole treatment period. An additional six rooms are devoted to patient preparation before irradiation. A schematic view of the HIMAC and the new treatment facility are shown in Fig. 3.

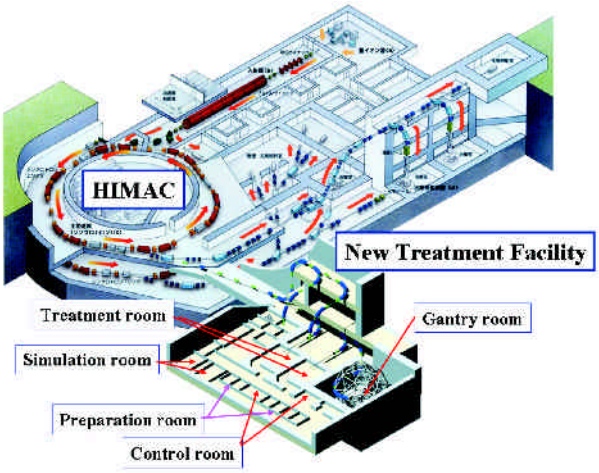

Fig. 3. Schematic view of the HIMAC and the new treatment facility.

2) Related R&D work

a) Development of the HIMAC accelerator

The beam intensity from the HIMAC synchrotron has been increased in order to complete one fractional irradiation with one cycle of synchrotron operation. In this case, the efficiency of the gated irradiation will be increased by extending the flattop duration, which will save considerable irradiation time. In order to increase the beam intensity, we have carried out a ture survey during beam injection in which we found that the 3rd-order coupling resonance caused beam loss. This resonance was corrected by four sextupole magnets, and the beam lifetime was increased more than 5-fold. Further, we tried multi-harmonics operation of the RF acceleration system in order to suppress the space-charge effect after bunching. This operation increased the acceleration efficiency by around 40%. Consequently, around 2×10^{10} carbon ions can be accelerated to the final energy. This intensity is sufficiently high to irradiate almost all tumors treated with HIMAC when using the 3D-scanning method with beam-utilization efficiency more than 90%. The extended flattop operation was successfully tested at the HIMAC synchrotron. In the raster scanning experiment, using an extended flattop, the total irradiation time was considerably decreased to 20 s from 40 s under the routinely used operation period of 3.3 s. Further, the beam profiles during the extraction duration of 100 s were measured by a multi-wire proportional counter in the high-energy beam-transport line. Analysis of the measurement results showed that both the position and the size for the extraction duration of 100 s were stabilized within ±0.5 mm at the iso-center.

b) Development of the irradiation method

In HIMAC treatments, we have observed a shrinkage of the target size, and a change of its shape during the entire treatment. In order to keep the sophisticated conformations of the dose distributions even in such cases, treatment planning has been required to be carried out just before each fractional irradiation ; this is called adaptive therapy. For this purpose, 3D scanning with a pencil beam should be employed, because it does not use any bolus or patient collimators, which take a long time to be manufactured. It is also well-known that 3D scanning has brought about high treatment accuracy in the case of a fixed target. However, this method has not yet been applied in practical use to treating a moving target with breathing in practical use. Therefore, we have developed the PCR method to treat a moving target. In 3D pencil-beam scanning, an interplay effect between the scanning motion and the target motion brings about hot and/or cold spots in the target volume, even in using the gated irradiation method, because the sizes of the distal and lateral dose profiles of the pencil beam are comparable to the residual motion range. The PCR method, therefore, which is combined with the rescanning technique and gated irradiation, is employed in order to avoid producing hot/cold spots. In the PCR method, rescanning on a slice is completed during one gate generated in the respiration period of the patient's breathing. Since the moving target position is averaged in both the lateral and distal directions, the hot and/or cold spots are not produced. The rescanning method requires a relatively large number of scans, which cause a relatively long irradiation time. Based on the uniform time structure of a beam extracted from the HIMAC synchrotron, we have thus developed a novel optimization technique for fast scanning in order to shorten the irradiation time, in which extra exposure during the transition of each spot is taken into account. The simulation study results showed that the PCR method gave a feasible solution in which a dynamic beam-intensity control technique based on the RF-KO

slow extraction method plays an important role to adequately control the phase correlation under a relatively small number of rescanning procedures. We noted in the PCR method that the irradiation time for each depth slice should be adjusted to within 1-2 s of the respiration gate duration. Consequently, we obtained a feasible solution for a moving target irradiation by the fast raster scanning method with rescanning and gating functions.

Since fast raster scanning is one of the key technologies for the PCR method, we carried out a fast raster scanning experiment by using the HIMAC spot scanning test line. At the present stage, we have adapted the measured dose response of the pencil beam with an energy of 350 MeV/n, corresponding to a 22-cm range in water. The beam size at the entrance and the width of the Gaussian-shaped mini-peak were 3.5 and 4 mm at one standard deviation, respectively. The validity of the beam model and the optimization calculation had already been verified experimentally. Using the dynamic intensity control system, we kept the beam intensity almost constant during irradiation. In the experiment, according to the treatment planning, we irradiated so as to produce a uniform biological dose distribution. It was verified that the measured dose distributions were in good agreement with the treatment planning as shown in Fig. 4.

(a) (b)

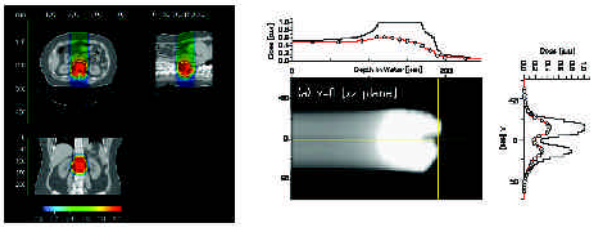

Fig. 4. (a) Treatment planning. (b) Measured physical-dose distribution (shown by circles) and the biological dose distribution (solid line) calculated from the measured physical-dose distribution.

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3.3. Standardization and Improvement of Therapeutic and Diagnostic Techniques

Tadashi Kamada, M. D., Ph. D.
Head, Hospital

Outline of Research Career

Dr. Kamada received a Ph. D. from Hokkaido University in 1996 for his study on radiotherapy of bile duct cancer. He has had 28 years of experience in clinical reseach on radiation oncology, including 13 years experience in carbon ion radiotherapy at NIRS. Since 2006, he has been group leader of the diagnosis and treatment advancement research group for standardization and improvement of therapeutic and diagnostic techniques.

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Objectives

- Development of software to create integrated clinical images, determine early therapeutic effects and analyze prognostic factors using a combination of multiple diagnostic imaging techniques.
- Improvement of treatment plans by using integrated images obtained from advanced dynamic imaging devices such as 4D CT.
- Research and development for indicators of quality standards and methods for quality control and assurance of particle beam and photon beam therapies and of diagnosis using radiation.
- Advancement and standardization of therapeutic and diagnostic methods based on investigation of medical radiation exposure in Japan.

Progress of Research

The Diagnosis and Treatment Advancement Research Group for standardization and improvement of therapeutic and diagnostic techniques consists of the Image Diagnosis Research Team, Image Processing Research Team, Quality Control Research Team and Radiological Protection Research Team. The group performs research on the advancement and standardization of radiation therapy and diagnostic methods. Progress of research in each team is summarized below.

1) Image Diagnosis Research Team

We have studied fundamentals of application of new PET tracers for clinical diagnosis. The main targets of our interests were imaging of cell/tissue metabolic indicators leading to better understanding of treatment effects especially of carbon ion radiotherapy.

We made a preliminary assessment to determine if Cu-62 labeled diacetyl-bis (N (4) -methylthiosemicarbazone); (Cu-62-ATSM) imaging of tumor hypoxia is associated with C-11-methionine imaging of amino acid metabolism in cervical cancer. PET/CT was performed in ten patients with cervical cancer for evaluation of both tumor hypoxia using Cu-62-ATSM and amino acid metabolism using C-11-methionine (MET). Patients had been histologically confirmed to have six squamous cell carcinoma and four adenocarcinoma. All necessary PET/CT studies were undergone before any treatment. Distribution of Cu-62-ATSM in tumor was compared with that of MET using the fused images registered automatically by PMOD software based on Mutual Information. The two-group system was used to evaluate the distribution of uptake as matched (mostly matched with each other) and mismatched (with each other). Tumor uptake of each tracer was also analyzed by the semi-quantitative index, tumor-to-normal-tissue-ratio (TNR). In our cases, matched and mismatched-groups totaled 1 case (10%) and 9 cases (90%), respectively. In the mismatched-group, Cu-62-ATSM tended to accumulate around the distal margin of the high MET uptake area in the tumor. This might represent different metabolic information of tumor. Mean TNR was 9.3 for MET and 3.8 for Cu-62-ATSM, and thus image contrast between tumor and surrounding normal tissue was higher in MET PET/CT images than in Cu-62-ATSM PET/CT images. We concluded that Cu-62-ATSM and MET had different distributions in most cases of cervical cancer. Cervical cancer had a greater tendency to uptake MET than Cu-62-ATSM and so the image contrast in MET PET/CT was higher than that of Cu-62-ATSM.

We studied the use of FDG-PET/CT to predict prognosis of patients with pancreas cancer treated by carbon ion radiotherapy. FDG-PET/CT was performed in 18 patients with pancreas cancer before CIRT, and 14 of them were received FDG-PET/CT one month after completion of CIRT. The average patient age was 64.4 years (range 48 to 77 years). Patients were followed for 3.5 to 38.4 months (mean 11.7 months)

after CIRT. FDG uptake was measured semi-quantitatively using the average SUV. The tumor SUV and change of SUV after CIRT were compared statistically with local recurrence rate, metastatic rate and result of prognosis by Kaplan-Meire analysis. In our cases, mean tumor SUVs before and after CIRT were 6.4 and 4.7, respectively. SUV at one month after completion of CIRT did not seemed to be significantly reduced, but there was a significant difference in tumor SUVs between before CIRT and after CIRT ($p=0.0036$), Patients with baseline SUV $\geqq$ 7.4 had significant higher local recurrence rates than patients with baseline SUV $<$ 7.4 ($p=0.0057$). Patients with baseline SUV $\geqq$ 9.2 had significant higher metastatic rates than patients with baseline SUV $<$ 9.2 ($p=0.0022$). Patients with baseline SUV $\geqq$ 9.2 had significant better prognosis than patients with baseline SUV $<$ 9.2 ($p=0.0053$). SUV after CIRT and change of SUV between pre and post CIRT showed no statistical difference in any factors. We concluded that FDG uptake before CIRT was a successful predictor of local recurrence rate, metastatic rate and survival in patients with pancreas cancer treated by CIRT. It seemed to be somewhat too early to evaluate therapeutic effect at one month after CIRT.

F-18-FLT PET imaging for head and neck cancer was started to assess carbon ion radiotherapy effect in cooperation with the diagnostic imaging group of Molecular Imaging Center.

One of our PET/CT systems was updated to use LSO detectors and 16- row MDCT.

2) Image Processing Research Team

The Image Processing Research Team analyzed organ movement during respiration using 4D CT applied to patients with lung carcinoma. The second model of the 256MSCT was based on the design of the first, which used a wide-area cylindrical 2D detector incorporating present CT technology mounted on the gantry frame of a 16-slice CT (Aquilion, Toshiba Medical Systems). The 256MSCT has 912 (transverse) $\times$ 256 (cranio-caudal) elements, each approximately 0.5 mm $\times$ 0.5 mm at the center of rotation. The 128 mm total beam width allows the continuous use of several collimation sets. SI coverage is 128 mm per rotation. Rotation time is 0.5 s/rotation and dynamic range is 18 bits. The detector element consists of a Gd2O2S ceramic scintillator and a single-crystal silicon photodiode, as used for MSCT. This characteristic allows for reconstructions in multiple planes that can also be displayed in a cine loop, which has not been hitherto possible. Since the 256MSCT provides both high spatial and high temporal resolutions, it is useful for reducing uncertainty in the RTP process.

Fourteen in-patients with qualifying lung adenocarcinoma or carcinoma were selected at random from among patients receiving carbon beam radiotherapy in our hospital. They gave informed consent to participate in the study, which was approved by the Institutional Review Board of the NIRS.

Volumetric cine imaging of the lung satisfactorily obtained continuous movement of the tumor in the sagittal section. Observation was facilitated by superimposition of the sagittal image at PE on images at each respiratory phase. Motion artifacts due to breathing were frozen by a temporal resolution of 250 ms, allowing the tumor shape to be evaluated accurately. Moreover, the thin slice thickness and short total acquisition time (approximately 6 s) helped determine target margins without the banding artifact which is slices with positions corresponding to the inconsistencies, observed with 4DCT obtained using conventional MSCT. Further, motion of the chest wall was smaller than that of the lung tumor and diaphragm. For all patients, average iso-center displacement relative to that at peak exhalation was 1.9 mm (range 0.2-5.4 mm) in the LR, 4.0 mm (range 0.7-6.8 mm) in the AP and 10.3 mm (range 2.5-24.7 mm) in the SI directions. Average internal margins for left, right and superior directions are small, those for anterior and posterior directions are the same value 3.5 mm, and that for the inferior direction is 21.0 mm.

The 256MSCT significantly improves the observation of tumor displacement and overcomes some of the limitations of present CT methods. Moreover, owing to its accurate determination of the margin, volumetric cine scanning is a useful complement to current irradiation methods.

3) Quality Control Research Team

Due to frequent radiotherapy accidents, the importance of quality control in radiotherapy has been increasingly recognized. The Quality Control Research Team of NIRS tries to meet the expectations for safe and reliable radiotherapy through the dosimetric research.

NIRS has been the Secondary Standard Dosimetry Laboratory (SSDL) for radiotherapy in Japan. The NIRS standard ionization chambers have been calibrated in terms of ^{60}Co exposure by the National Metrology Institute of Japan. More than 700 therapy-level dosimeters from hospitals were calibrated with the NIRS standard chambers and the ^{60}Co standard field in the last fiscal year. The quality control research team is preparing to establish the standard field of absorbed dose to water and has calibrated the NIRS standard chambers in terms of absorbed dose to water, in collaboration with the International Atomic Energy Agency (IAEA).

To establish a nation-wide dosimetry audit system in radiotherapy, the quality control research team carried out comparative studies between the glass dosimeters and TLDs (thermoluminescence dosimeters) which had been used as a postal dosimeter. The results showed that the glass dosimeter features were appropriate for the postal dose audit. The team carried out a pilot study in which postal glass dosimeters were sent to hospitals in Japan. The pilot study showed 1.3 % standard deviation of dose among 100 responding hospitals. In November 2007, the regular dosimetry audit service for radiotherapy facilities was been started using the glass dosimeter with a commercial base by the Association for Nuclear Technology in Medicine, in collaboration with the National Cancer Center and NIRS.

In addition to the above activities as SSDL, the quality control research team has also carried out the studies with regard to dosimetry for HIMAC. The team has developed a graphite calorimeter for absolute absorbed dose measurement. The preliminary calorimeter measurement showed good agreement with the ionization chamber measurements for ^{60}Co. On the other hand, the absorbed dose obtained by the calorimeter was approximately 3 to 4 % higher than that by the ionization chamber for carbon beams. The disagreement seems to arise from the w-value uncertainty for the carbon beams.

From the viewpoint of microdosimetry, tissue-equivalent proportional counters (TEPCs) are used to study the estimation of the clinical dose at HIMAC. The RBE values for carbon beams are obtained by the microdosimetric kinetic model (MKM) and spectra measured with the TEPCs. The absorbed dose obtained by the TEPCs agreed with that obtained by an ionization chamber. The TEPC measurement is expected to be useful for experimental estimation of the clinical dose.

These activities are expected to influence other radiotherapy facilities in Japan as well as the NIRS. The quality control research team also intends to contribute to the field of radiotherapy internationally in cooperation with organizations such as the Forum for Nuclear Cooperation in Asia (FNCA), IAEA, World Health Organization (WHO) and International Organization for Standardization (ISO).

4) Radiological Protection Research Team

a) Dose estimation and protection against medical radiation

As one of the studies on radiation protection to medical exposures for patients, organ doses of CT on PET/CT examinations were estimated by the measurements using TDLs and an adult anthropomorphic phantom for the X-ray CT apparatus practically used in hospitals. Set parameters such as current could be selected in one CT apparatus, and the organ doses were varied over a wide range, from under 10 to over 40 mGy, according to the set conditions. The data showed that the effective doses as external exposures from CT in PET/CT examinations were, in general, greater than internal exposures of PET although the doses of some source organs of PET internal exposures were not always so low compared to those of CT. a

We also conducted measurements of the organ doses of X-ray CT examinations for three typical X-ray CT apparatuses produced by different manufacturers. We used the TDLs and an adult anthropomorphic phantom as the values of normalized organ doses per mAs and effective mAs for the factors. The differences in organ doses between the highest and lowest were approximately 2-fold. The organ dose variations among apparatuses of different manufactures could be explained in part of the half-value layers (HVLs). The results suggested that the organ doses could differ depending on the kinds of apparatuses even though the same X-ray CT examinations would be performed.

From the viewpoint of radiation protection to medical staff members as occupational exposure, we began the measurements of neutrons produced in the heavy ion therapy facility as part of a study on the radiation protection and management of heavy ion therapy facilities. We could get data on the doses of neutrons irradiated from activated equipment or from patients for the staff members ; these data included energy spectra and spatial distribution information.

b) Survey of medical exposure

We have analyzed data on frequency and conditions of X-ray CT examinations performed last year, and started the next nationwide survey dealing with general X-ray examinations. There are more than 9,000 hospitals and about 100,000 clinics which are survey targets. Questionnaires have been made for the survey and they cover patient information such as sex and age, and about the equipment, frequencies, conditions etc. being used in the fascilities.

Major Publications

1) S. Mori, T. Obata, H. Katou, R. Kishimoto, S. Kandatsu, S. Tanada, M. Endo : Preliminary study : Color Map of Hepatocellular Carcinoma Using Dynamic Contrast-Enhanced 256-Row Detector CT, European Journal of Radiology, 62 (2), 308-310, 2007
2) H. Mizuno, T. Kanai, Y. Kusano, S. Ko, M. Ono, A. Fukumura, K. Abe, K. Nishizawa, M. Shimbo, S. Sakata, S. Ishikura, H. Ikeda :

Feasibility study of glass dosimeter postal dosimetry audit of high-energy radiotherapy photon beams, Radiother. Oncol. 86 (2), 258-63, 2008

3) S. Mori, K. Nishizawa, C. Kondo, M. Ohno, K. Akahane, M. Endo: Dose of Radiation Exposure to Subjects in Computed Tomography Cardiac Imaging with 16-, 64- And 256-Multislice CT Scanners. Eur J Radiol 65 (3) 442-8, 2008.
4) K. Nishizawa, S. Mori, M. Ohno, N. Yanagawa, T. Yoshida, K. Akahane, S. Wada, K. Iwai : Patient dose estimation for multi detector-row CT examination. Radiat. Protect. Dosim 128 (1) 98-105, 2008
5) K. Nishizawa, Y. Masuda, K. Morinaga, S. Suzuki, S. Kikuyama, T. Yoshida, M. Ohno, K. Akahane, K. Iwai : Surface dose measurement in patients and physicians and effective dose estimation in patients during uterine artery embolization. Radiat. Protect. Dosim 128 (3) 343-50, 2008

3.4. RadGenomics Project for Radiotherapy

Takashi Imai, Ph.D.
Director, RadGenomics Research Group

Outline of Research Career

Dr. Imai received a Ph.D. from the University of Tsukuba in 1986. Following a fellowship from the Japan Society for the Promotion of Science for Japanese Junior Scientists at the Institute of Applied Biochemistry, University of Tsukuba, he joined the Tsukuba Life Science Center, Institute of Physical and Chemical Research (RIKEN). From 1988 to 1989, he worked in the Department of Genetics, Washington University Medical School (St. Louis, Missouri, USA) as a visiting research associate. Here Professor Maynard Olson sparked his interest in the human genome project. After joining The Cancer Institute, (Japanese Foundation for Cancer Research) in 1991, Dr. Imai worked on cancer and population genomics. He moved to NIRS in 1994. From 2001 to 2006, he worked as the project leader of the RadGenomics Project. Since 2006 he has been the director of the RadGenomics Research Group.

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Objectives

Normal tissue reactions of cancer patients vary considerably after radiotherapy. A number of observations have indicated that certain genetic factors play important roles in this variability. The aim of the RadGenomics Research Group is to explore the genetic characteristics of both the patient and the bearing tumor, by which the potentially most effective radiotherapy can be delivered. From a molecular-biological standpoint, this will open the way to the development of an individual-oriented radiotherapy. The project will also contribute to future research on the molecular mechanisms of radiation sensitivity in humans.

Progress of Research

1) Patients

Between 2001 and 2008, 2,327 patients were registered including 748 breast cancer patients, 309 cervical cancer patients, 624 prostate cancer patients, and 269 head and neck cancer patients. Normal tissue reactions until the 3rd month after completion of the treatment were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI/CTC). Late effects on normal tissues were graded according to the Radiation Therapy Oncology Group/ the European Organization for Research and Treatment of Cancer (RTOG/EORTC) scoring system and the Late Effects of Normal Tissues-Subjective, Objective, Management and Analytic (LENT-SOMA) scoring system. Patients were divided into two groups (radiosensitive and radioresistant) according to the grades determined by the above scoring systems.

2) Haplotype-based analysis of genes associated with risk of adverse skin reactions after radiotherapy in breast cancer patients

Objective : To identify haplotypes of single nucleotide polymorphism markers associated with the risk of early adverse skin reactions (EASRs) after radiotherapy in breast cancer patients.

Methods and materials : DNA was sampled from 399 Japanese breast cancer patients who qualified for breast-conserving radiotherapy. Using the NCI/CTC scoring system, version 2, the patients were grouped according to EASRs, defined as those occurring within 3 months of starting radiotherapy (Grade 1 or less, n = 290 ; Grade 2 or greater, n = 109). A total of 999 single nucleotide polymorphisms from 137 candidate genes for radiation susceptibility were genotyped, and the haplotype associations between groups were assessed.

Results : The global haplotype association analysis ($p < 0.05$ and false discovery rate < 0.05) indicated that estimated haplotypes in six loci were associated with EASR risk. A comparison of the risk haplotype with the most frequent haplotype in each locus showed haplotype GGTT in CD44 (odds ratio [OR] = 2.17 ; 95% confidence interval [CI], 1.07-4.43) resulted in a significantly greater EASR risk. Five haplotypes, CG in MAD2L2 (OR = 0.55 ; 95% CI, 0.35-0.87), GTTG in PTTG1 (OR = 0.48 ; 95% CI, 0.24-0.96), TCC (OR = 0.48 ; 95% CI, 0.26-0.89) and CCG (OR = 0.50 ; 95% CI, 0.27-0.92) in RAD9A, and GCT in LIG3 (OR = 0.46; 95% CI, 0.22-0.93) were associated with a reduced EASR risk. No significant risk haplotype was observed in REV3L.

Conclusion : Individual radiosensitivity can be partly determined by these haplotypes in multiple loci. These findings may lead to a better understanding of the mechanisms underlying the genetic variation in radiation sensitivity and resistance among breast cancer patients.

3) Radiation-induced cell-death signaling pathway activation by concurrent use of cisplatin in sequential biopsy specimens from patients with cervical cancer

Objective: To identify changes in gene expression related to the concurrent use of platinum compounds with radiotherapy, in the treatment of cervical cancer.

Patients and methods: Biopsy specimens were obtained from 39 patients with squamous cell carcinoma of the uterine cervix, before and during fractionated radiotherapy. Twenty patients were treated with radiotherapy (RT) alone, while 19 received the same radiotherapy plus concomitant chemotherapy with cisplatin (CRT). Changes in gene expression induced by treatment were investigated using single-color oligo-microarrays consisting of 44K human sequences. Paraffin-embedded samples were used to examine apoptosis and the expression of protein by treatment-responsive genes. Changes in mRNA expression were assessed for these genes by real-time reverse transcriptase-polymerase chain reaction. Aberrant genomic change (detected using microarray-based comparative genomic hybridization), human papilloma virus infection, and p53 status were also evaluated.

Results: The expression of CDKN1A, BAX, TNFSF8, and RRM2B was consistently up-regulated by CRT (9 Gy with a single administration of cisplatin). Similar expression changes were induced by RT (9 Gy) alone, although the variability between tumors was greater. Apoptotic cells were significantly increased in both groups. CRT significantly increased the numbers of cases with diffusely distributed CDKN1A-positive cells. Genetic losses at 2q33-ter and gains of 3q26-ter were detected in the samples with high frequency; 60% were positive for human papilloma virus DNA; and three tumors had deletions/mutations of the p53 gene. There was no difference in the incidence of these genomic changes between the groups, and no association was found with the changes in expression of CDKN1A, BAX, TNFSF8 or RRM2B.

Conclusions: Using biopsy samples from pretreatment and midtreatment cervical tumors, we identified therapy-induced genes related to the cell death signaling pathway. CRT produced a homogenous pattern of changes in expression of known radiation-responsive genes.

4) Chemoradiation-induced expression of fibroblast growth factor-2 and laminin in patients with cervical cancer

Objective: To investigate the protein expression change of FGF2 in cervical cancers during chemoradiotherapy, as indicated in our previous study using microarray analysis. In addition, we sought to examine the predictive value of such changes in expression for disease failure after chemoradiotherapy.

Patients and methods: Biopsy specimens were obtained from 35 patients with cervical cancers before (pretreatment) and 1 week after initiation (midtreatment) of chemoradiotherapy (CRT) (9 Gy and 40 mg/m (2) of cisplatin). Immunohistochemical studies (IHS) were performed to detect FGF2, laminin and CD44 expression using an automated streptavidin-biotin immunoperoxidase staining system. Positive area proportion (%) of FGF2 and CD44 were analyzed using an image analysis system and laminin staining pattern was scored by continuity of the basement membrane immunopositivity. Patients were defined as good ($n = 18$) or poor responders ($n = 10$) based on their two-year disease-free survival.

Results: Protein expression of FGF2 in midtreatment samples (mid) was significantly higher than in pretreatment samples (pre). Discontinuity of laminin staining pattern in mid was significantly higher than in pre. Protein expression of CD44 was not significantly different between mid and pre. The ratio change (mid versus pre) of FGF2 expression in poor responders was significantly lower than that in good responders ($p < 0.05$). The number of cases with discontinuity of laminin staining pattern at pre was significantly increased in the poor responders ($p < 0.05$). Ratio changes of FGF2 or CD44 expression in mid correlated with laminin staining pattern in pre.

Conclusions: Using biopsy specimens from pretreatment and midtreatment cervical cancers, we revealed significant changes in FGF2 protein expression during fractionated radiotherapy with cisplatin. We also found that FGF2 ratio change and laminin discontinuity staining pattern at pretreatment were significantly associated with prognosis. These molecular features might help us to identify patients at high risk of disease failure after CRT.

5) Up-regulation of stress-response genes with cell cycle arrest induced by carbon ion irradiation in multiple murine tumors models

Objective: To elucidate the in vivo biological effects induced by carbon-ion irradiation using comprehensive expression analysis.

Materials and methods: We examined gene expression changes after carbon-ion (C-ion) irradiation (290 MeV/m, SOBP 6 cm middle, 50 kev/μm) with a single dose of 30 Gy in four mouse tumors (NR-S1, SCCVII, NFSa and #8520) transplanted into the hind legs of C3H/HeNrs mice, using 44K single-color oligo-microarrays at six hours (h), one day and three days after irradiation. Gamma rays of 30 Gy and 50 Gy were used as a reference beam. Identification of C-ion-responsive genes was based on a false discovery rate of <5% using the Wilcoxon test ($p < 0.001$) and the Benjamini-Hochberg correction.

Results: In all tumors, the level of expression of several tens of genes, including Ccl3, Ccng1, Cd80, Cdkn1a, Cxcl2, IL7r, Lrdd, Mgmt, Mmp8 and Polk, was significantly altered 6 h and day 1 following C-ion irradiation. At day 3, several hundred genes, many of which are also classified as stress-response or cell-communication genes, including Tnfrsf5, Ikbke and Icam1, were up-regulated following C-ion irradiation. The expression level of the majority of these genes was similar following gamma-ray treatment, although the change was not as extensive and intertumor variance was apparent. Several genes, including Ikbke, Serpina3n and Saa3, responded differentially following C-ion irradiation than after gamma-ray irradiation. Pathological investigation and immunohistochemical analysis of Cdkn1a revealed cell cycle arrest with mitotic catastrophe in tumors irradiated by C-ions.
Conclusions : This study revealed significant C-ion induced up-regulation of stress-responsive and cell-communication genes common to different tumor types. These findings provide evidence for the efficacy of this modality for the treatment of local tumors.

6) Visible haplotype-tag SNP typing array device for human radiation sensitivity-associated genes
Objective : To develop a visible genotyping array device for eight haplotype-tag SNPs in two genes (PTTG1 and CD44) using previously established methodology.
Methods and materials : Haplotypes of multiple genes have been reported to be associated with risk of adverse skin reactions after radiotherapy in breast cancer patients. The developed device uses an allele-specific extension reaction of covalently immobilized oligonucleotide primer to discriminate nucleotides at SNP sites. Each primer oligonucleotide has a 3'-end locked acid nucleotide modification to enhance its allelic specificity. Biotin-dUTPs provided in the reaction mixture are selectively incorporated only to the extenting oligonucleotides, enabling their use as tags for the following streptavidin-conjugated alkaline phosphatase-mediated colored precipitation of substrates onto the surface of the array. Resulting colored spots on the device can be observed by the naked eye and conveniently recorded by a digital camera that is commercially available at reasonable cost.
Results : Allelic discrimination of all immobilized oligonucleotides was validated using 45 reference individuals previously genotyped by the MassARRAY system. Reliability of genotyping by this device was quantitatively assessed by calculating Silhouette score and resulting scores of all SNPs were proven to be beyond the cut off value of 0.65. The eight haplotype-tag SNPs can be simultaneously analyzed in a single reaction mixture within a few hours and multiple samples up to four can be analyzed simultaneously on a single device whose surface area is divided by a water-proof multiwell seal.
Conclusion : This visible haplotype-tag SNP typing array device has expected benefits of convenient usage at reasonable cost and thus it should provide easy access for bedside clinical diagnosis of radiation sensitivity.

7) Gene expression analysis in human malignant melanoma cell lines exposed to carbon beams
Objective : To elucidate the molecular changes in response to carbon beams (C-ions) in melanoma.
Materials and methods : We examined expression profiles of 6 melanoma cell lines exposed to C-ions or X-rays with 2 Gy using single-color microarrays.
Results : Twenty-two genes, including nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (NFKBIA), responded to C-ions in all six cell lines, based on analysis of variance (ANOVA) filtering ($p < 0.001$). We found 173 genes that responded in common to C-ions in four cell lines. We identified many down-regulated genes including the cell cycle - related genes that were more responsive to C-ions than X-rays. In contrast, most of the up-regulated genes including the tumor protein p53 (p53) target genes responded to both C-ions and X-rays. C-ions induced G2/M arrest significantly more than X-rays at 30 h ($p < 0.05$).
Conclusion : Our findings suggest that down-regulation of gene expression plays a key role in the response to C-ions. Regulation of cell cycle - related genes and induction of prolonged G2/M arrest may be responsible for the extra sensitivity to C-ions, whereas p53-related genes may have similar roles in the sensitivities to both C-ions and X-rays.

8) Prediction of lymphatic metastasis based on gene expression profile analysis after brachytherapy for early-stage oral tongue carcinoma
Objective : To evaluate the predictive ability of lymphatic metastasis after brachytherapy (BRT) for early-stage tongue carcinoma based on gene expression profiling since the management of lymphatic metastasis of early-stage oral tongue carcinoma patients is crucial for its prognosis.
Patients and methods : Pre-therapeutic biopsies from 39 patients with T1 or T2 tongue cancer were analyzed for gene expression signatures using Codelink Uniset Human 20K Bioarray. All patients were treated with low dose-rate BRT for their primary lesions and underwent strict follow-up under a wait-and-see policy for cervical lymphatic metastasis. Candidate genes were selected for predicting lymph-node status in the reference group by the permutation test. Predictive

accuracy was further evaluated by the prediction strength (PS) scoring system using an independent validation group.
Results : We selected a set of 19 genes whose expression differed significantly between classes with or without lymphatic metastasis in the reference group. The lymph-node status in the validation group was predicted by the PS scoring system with an accuracy of 76%.
Conclusions : Gene expression profiling using 19 genes in primary tumor tissues may allow prediction of lymphatic metastasis after BRT for early-stage oral tongue carcinoma.

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4) K. Imadome, M. Iwakawa, K. Nojiri, et al : Upregulation of Stress-response Genes with Cell Cycle Arrest Induced by Carbon Ion Irradiation in Multiple Murine Tumors Models., Cancer Biol Ther, 7 (2) : 205-214, 2008
5) Y. Michikawa, T. Suga, A. Ishikawa, Y. Ohtsuka, M. Iwakawa, T. Imai : Visible Haplotype-tag SNP Typing Array Device for Human Radiation Sensitivity-Associated Genes, In Oligonucleotide Array Sequence Analysis, Nova Science Publishers, pp3-14, 2008

3.5. Biological Research Concerning the Improvement of Radiation Therapy

Ryuichi Okayasu, Ph. D.
Director, Heavy-Ion Radiobiology Research Group

Outline of Research Career

Dr. Okayasu received his Ph.D. in radiation biology from Colorado State University, USA in 1987 and worked as a post-doctoral fellow at Thomas Jefferson University, Philadelphia and MD Anderson Cancer Center, Houston. Next he took a position at Columbia University as an associate research scientist. In 1995, he moved to the University of Texas Medical Branch at Galveston as an Assistant Professor and then onto Colorado State University. In 2002, he moved back to Japan to become a team leader at the International Space Radiation Laboratory (ISRL), NIRS and in 2005 he was appointed as Director of ISRL. In 2006, he was transferred to the Research Center for Charged Particle Therapy and became Director of Heavy-Ion Radiobiology Research Group.

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Objectives

There are three mid-term plans for this group. These are: 1) to provide biological experimental data for analyzing clinical data with regard to tumor control ratio and normal tissue responses for various radiation therapy protocols; 2) to estimate the risk and benefit ratio between tumor cell killing and normal tissue sparing by theoretical calculations based on patients' dose distribution as well as experimental data on cell and animal studies; and 3) to propose a more efficient radiation therapy regimen by comparing heavy ion radiotherapy and other radio-therapy protocols such as use of X-rays. Specific points to be addressed under plan 3 are: 3a) to explore radio-sensitizers and protectors which could be used with heavy ion radiotherapy; 3b) to elucidate the mechanism of effective heavy ion treatment for hypoxic tumor cells which show strong resistance to radiation; 3c) to study the indirect (bystander) effects of radiation which occur in non-irradiated cells adjacent to irradiated cells; and 3d) to integrate the above proposals to improve radiation therapy and accumulate the biological data resources for a new cancer therapy. These objectives are studied by four teams including 1) Biophysics Team, 2) Experimental Therapy Team, 3) Cellular and Molecular Biology Team and 4) Radiation Modifier Team. Each team has different individual objectives, however, co-operation among the four teams is sought in order to accomplish the goals of this group.

Progress of Research

1) Biophysics Team

The long term goal of this team is to study how to kill cancer cells effectively without affecting normal tissues using heavy ion irradiation. The fact that cells have a potential to repair radiation-induced DNA damage is an important factor. We studied LET dependency of chromosomal aberrations induced before and after the repair period. We also studied the relationship between the initial DSB, the non-repairable DSB and the cell killing under oxic or hypoxic conditions. From these studies, we found a higher RBE value for chromosomal aberration before the repair period than after the period. We also found a lower repair efficiency of DNA double-strand breaks (DSBs) in hypoxic conditions than in oxic conditions.

We are developing a useful model for RBE calculations from the physical characteristics of ion beams. We biologically verified the micro-dosimetric kinetic model and the local effect model with our cell survival data. The difference between the two models is primarily the result of different approaches calculating the biological effects of the extremely high local dose in the center of the ion track.

The geometric locations of ion traversals in mammalian cells constitute important information in the study of heavy ion-induced biological effects. We employed a contact microscopy technique which enables us to visualize cells on a plastic track detector and to plot positions of ion traversals.

The bystander effect is another important factor that affects biological end points induced by radiation. GJIC is an important function of cells, and is believed to have beneficial effects in anti-tumor therapy. When cancer cells were irradiated with ion beams, micronuclei, cell-cycle arrest, and cell killing were induced in dose dependent manners. Those damages in GJIC-enhanced cell populations were decreased, and the damages in suppressed populations were increased more than for untreated cells. These results indicate that the bystander effect may be involved in GJIC-mediated radioprotection of cells, which may have implications for radiotherapy.

2) Experimental Therapy Team :

It was determined that the RBE values by carbon ions at three different LET values 15, 45, 75 keV/μm were 0.6, 1.0 and 1.4, respectively, when calculated at a 20% tumor formation frequency of irradiated mice. Furthermore, to determine the ratio of cells with two different radio-sensitivities, we collaborated with another group using a cytogenetic method with fluorescence protein. We are also working on detecting the ratio of cells with various sensitivities in vivo, and have gotten a better idea how to achieve this goal by using in vitro colony assay data.

To investigate the relationship between LET and skin reaction, we have performed fractionated mono-peak irradiation on the normal mouse foot. The α/β ratios were 28 Gy, 39 Gy, and 38 Gy at the LET values for 58, 13.6 keV/μm and γ rays, respectively. There seems to be no significant difference among the α/β ratios.

3) Cellular and Molecular Biology Team

Biological differences between X-ray and heavy ion particle (C, Fe, Ne) irradiations were investigated using several quantitative assays such as γH2AX and PCC techniques. We also focused on the molecular mechanism in the early DNA damage responses with therapeutic level radiation doses. A comprehensive gene expression technique (HiCEP) using several irradiated several human cell lines demonstrated some characteristic molecular signatures toward different types of ionizing radiation (IR). A group of early responsive IR-induced genes (ATF3, BTG2, TP53INP1) in human cells remained active for a longer period with carbon ion beams than with X-rays. In addition, we successfully detected some common genes which were down-regulated by various types of IR.

We have demonstrated that cells irradiated with X-rays and heavy ion particles showed different radio-sensitivities depending on the cells' DNA repair characteristics ; in particular, homologous recombination (HRR) defective cells showed an extreme sensitivity to high LET heavy ion irradiation. Our result suggests that these different IRs induce different types of DNA damage. We are planning to further clarify the molecular mechanisms associated with heavy ion irradiation in order to support a successful clinical outcome.

4) Radiation Modifier Team

The radiation modifier team has studied three subjects and obtained the following results.

i) In order to develop better compounds for free radical scavengers, several resveratrol analogs were synthesized and analyzed. The kinetic study of their in vitro free radical scavenging reaction showed that introduction of methyl groups on the phenyl rings of resveratrol increased the scavenging rate constant significantly. Introduction of three methyl groups resulted in a rate constant more than 60 times larger than that of the original resveratrol. Analogs of artepillin C, an ingredient of propolis, were also examined and an analog having 2.4 times larger rate constant was found.

ii) The radioprotector, α-lipoic acid, was examined against the whole body Fe ion-irradiation (2.0 Gy). The cognitive dysfunction of mice caused by Fe ion-irradiation was ameliorated by the administration of α-lipoic acid before irradiation. Oxidative stress to DNA, proteins, and lipids in the cerebellum caused by Fe ion-irradiation was reduced by the administration of α-lipoic acid.

iii) Redox- and oxygen-mapping was studied in a test using free radical reactions in a gelatin sample irradiated by heavy ion beams. A reaction mixture containing glutathione and a nitroxyl radical, TEMPOL, was caked with gelatin, and then irradiated with 290 MeV/n carbon ion beams. Free radical reactions occurred in dose- and LET-dependent manners during carbon ion irradiation. The free radical yield obtained with heavy ion irradiation was expected to be less than 1/3 of that obtained with X-ray irradiation when the same dose for a deeper target organ was considered. In this experiment, both ESR and MRI methods were able to detect free radical generations in gelatin samples irradiated with heavy ion beams and showed similar results. Both ESR and MRI appear to be useful to visualize free radical reactions.

Major Publications

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low LET radiation in normal human cells. Mutat. Res. 652, 95-101, 2008.

3.6. Transcriptome Research for Radiobiology

Masumi Abe, Ph. D.
Director, Transcriptome Research Group

Objectives

This subject has been researched by the Transcriptome Research Group consisting of 3 teams : Stem Cell Research Team, Gene Expression Profilling Team, and Model Organism Research Team.

Progress of Research

1) Stem Cell Research Team

This team has been focused on germ stem cells ; the team's final goal is to understand the effect of radiation at an individual level not at a cellular level only.

It is known that several genes are expressed both in embryonic stem cells (ES) and germ stem cells. However, their function in germ cells is still unknown. Our team identified a new gene that expresses both in ES and spermatogonial stem cells (SSCs). They generated its knockout mice and found a severe defect in their spermatogenesis and an accumulation of SSCs in the mice. Further study revealed that the gene plays a role in the differentiation step of SSCs.

In addition, they are conducting a new project on iPS (induced pluripotent stem cells) to understand the molecular mechanism underlying their generation.

2) Gene Expression Profiling team

High coverage gene expression profiling (HiCEP) that we have developed is an ideal tool for transcriptome analysis, and it is based on a principle different from that for hybridization-based methods.

This year we attempted to improve the HiCEP method to allow it to analyze even a small amount of starting materials. At the beginning of HiCEP development, approximately 1 μg of polyA RNA was needed for the analysis ; however, subsequent improvement has allowed us to perform the analysis with a total RNA amount of 0.1 μg which corresponds to 10,000 mammal cells. This year we successfully developed a new protocol using less than 1 nanogram of total RNA, corresponding to less than 100 cells.

Applying this new protocol of HiCEP to single cell transcriptome analysis, which contains approximately 10 picogram of total RNA, we could observe about 5,000 transcripts, almost all of which were highly expressed. Now we are attempting to develop an analysis using fewer than 10 cells with high coverage detection.

Using HiCEP technology, we are conducting a new program for medical applications. The ethical committee of NIRS has authorized our proposal, and the first trial will be started soon.

3) Model Organism Research Team

This team has been basically supporting other research teams, especially the Stem Cell Research Team. Gene KO mouse technology has been shown to be working. A transplantation test for testicular cells to assess their ability for spermatogenesis is now available. The team is attempting to introduce technology for genome reprogramming using nuclear transfer.

4. Molecular Imaging Center

Iwao Kanno, Ph. D.
Director, Molecular Imaging Center

Outline of research career

Iwao Kanno started his professional career at Akita Research Institute of Brain and Blood Vessels in 1970, where he was an active researcher for 36 years. In 1977, he developed a custom radionuclide emission tomography system using a handmade rotational dentist chair. In 1979 in collaboration with Shimadzu, he developed a hybrid type of emission tomography which combined positron emission tomography (PET) and single photon emission computed tomography (SPECT). His efforts were also directed to developing methodology for quantitative assessment of physiological and biochemical parameters from PET and SPECT images.

Objectives

Progress in molecular biology has opened the window to understanding the molecular mechanisms of living healthy and diseased organs. Molecular imaging is a new interdisciplinary field that integrates imaging technology and molecular biology to help visualize molecular behaviors spanning the microscopic to macroscopic scales. Positron emission tomography (PET), magnetic resonance imaging (MRI) and optical imaging will provide clear and comprehensive images demonstrating molecular functions. The Molecular Imaging Center consists of four research groups, Diagnostic Imaging Group, Molecular Neuroimaging Group, Molecular Probe Group and Biophysics Group, and the Research Promotion Unit. The Molecular Imaging Center aims to image molecular functions of living animals in both healthy and diseased conditions. Of several methodologies for imaging molecular functions, the center covers in vivo molecular imaging from rodents to humans. It is already a world leader in the development of PET probes and technologies, and it also has invested efforts in other promising technologies such as MRI. Our primary goals are to move towards understanding the mechanism of brain function and cancer pathology and to use this knowledge in clinical applications.

Overview

The Diagnostic Imaging Group continued our clinical PET study with FLT, a marker of cell proliferation, in the evaluation of effectiveness of carbon ion radiotherapy in lung and head & neck cancer patients in collaboration with the Research Center for Charged Particle Therapy. A multi-center study of PET with ^{62}Cu-ATSM, a marker of tumor hypoxia, is also ongoing. To identify novel targets of mesothelioma, large-scale functional screening using siRNA was conducted and 39 genes were newly identified to have an anti-apoptotic function. We also found that cellular content of trace metals such as Mn and Cu is increased in various mesothelioma cells, indicating the possibility that these heavy metals are involved in the development and progression of mesothelioma. We established subcutaneous and orthotopic transplant model of fluorescent cancer cells in mice and evaluated the change of fluorescent intensity and uptake of various PET tracers in the tumor with/without treatment. Research on the development of an antibody probe for PET/SPECT tumor imaging was continued using anti-c-kit and anti-ERC/mesothelin monoclonal antibodies and a tumor xenograft was successfully imaged by In-111 labeled antibodies. Our investigation on the PET imaging of mesothelioma-bearing mice using FDG and FLT has shown that suitable PET tracers differ according to the histological subtypes. The study on the development of novel reporter gene imaging has moved to in vivo investigation. When ferritin heavy chain gene was electroporated into a subcutaneous tumor, significant reduction in signal intensity was observed on T2-weighted MR imaging.

The Molecular Neuroimaging Group carried out mapping of peripheral benzodiazepine receptors in Alzheimer's disease. A normal database for the pre- and postsynaptic dopaminergic functions in the living human brain using PET was constructed. Dopamine transporters in schizophrenia were measured using [^{11}C] PE2I and no significant difference was observed between schizophrenia patients and controls in any brain regions. Regional differences in receptor occupancy by antipsychotic drugs were investigated and no regional difference was found in occupancy of dopamine D2 receptors by an atypical antipsychotic drug. Clarification of molecular mechanisms linking imaging-based biomarkers and psychiatric symptoms by behavioral analyses was carried out. Further investigations of transgenic mouse models using PET

and [^{18}F]fluoroethyl-DAA1106 also revealed deleterious roles of activated microglia in the Alzheimer's disease pathogenesis. In vivo studies of monkeys and rats using PET and [^{11}C] MNPA, a novel agonistic PET tracer for dopamine D2 receptor, indicated that changes in the release of endogenous dopamine after pharmacological challenges are measurable in the living brains. Functional roles played by the central substance P neurotransmission system by in vivo imaging of substance P receptors were elucidated. [^{18}F] fluoroethyl-SPA-RQ measurements delineated consistency in the distribution of the central substance P receptors across species and potential utility of these animals for preclinical assessments of pharmaceutical agents targeting the substance P neurotransmission.

The Molecular Probe Group developed a probe for quantitative assessment of brain efflux function. Targeting multi-drug resistance-associated protein (MRP), we designed 6-halo-purine derivatives. A novel thymidine analog, 4'- [methyl-^{11}C] thiothymidine ([^{11}C] S-dThd), was further evaluated to assess DNA synthesis in tumor bearing rats. We found that [^{14}C] S-dThd is a promising marker for DNA synthesis. A practical route for preparing [^{18}F] ligand containing [^{18}F] fluorobenzene moiety by employing a reaction of diphenyliodonium salt with [^{18}F] F^- was adopted for the synthesis of ^{18}FDOPA under a no added carrier condition. [^{11}C] Acetyl chloride ([^{11}C] AcCl), prepared in a loop method by reacting methylmagnesium bromide with [^{11}C] CO_2 and followed by treatment with oxalyl choride, was applied for the preparation of [^{11}C] oseltamivir and its activated form ([^{11}C] Ro64-0802). A new labeling method generating ^{11}C-C bonds was developed by using [^{11}C]nitromethane. C-carboxylation of [^{11}C] nitromethane was accomplished from [^{11}C] methyl nitronate and 1-ethoxycarbonylbenzotriazole to afford [2-^{11}C] ethyl nitroacetate in a radiochemical yield of 75±6%. In vitro binding of [^{11}C] raclopride with ultra-high specific activity (SA) in the striatum and cerebral cortex of rat brain was characterized. The radionuclide ^{62}Zn was produced by the nuclear reaction ^{63}Cu (p, 2n) ^{62}Zn with the AVF cyclotron at NIRS. The ^{62}Zn/^{62}Cu generator was prepared remotely and distributed to three PET facilities (Fukui University, Yokohama City University, and the National Cancer Center). Four new PET radiopharmaceuticals ([^{11}C] MNPA, [^{11}C] AC5216, [^{11}C] Gefinitib, and [^{18}F] -labeled compound for β-Amyloid imaging) were released for the clinical use and approved by the Institutional Review Board at NIRS.

The Biophysics Group together carried out development of a patch antenna array (PAAC) RF coil for ultra-high magnetic field MRI. When imaging a human body using an ultra-high magnetic field MRI system, artifacts may be caused by the dielectric effect etc. induced by the shortness of the wavelength. It is difficult to create a big volume coil because of the short wavelength. Within the Physics Group, four individual teams carried out separate projects. The Magnetic Resonance Molecular Imaging Team was involved in the following developments : immunocyte labeling and tracking using manganese contrast agents ; development of multimodal probes using quantum-dots ; and in-vivo detection of reactive gliosis in the rat stroke model. The Biosignal Physiology Team covers two kinds of signals, human MRI data and animal two-photon microscopy data ; diffusion functional MRI, GSH-edited ^{1}H MRS for schizophrenia and new diffusion tensor parameter for cancer diagnosis etc. The Data Analysis Team developed and evaluated some new algorithms : omission of arterial blood sampling using an intersectional searching algorithm and clustering and a denoising algorithm for voxel-based model estimation using Wavelet transformation. However, it is difficult to conduct due to the small size of mice. The team is investigating an invasive system for arterial sampling from mice. The Imaging Physics Team demonstrated the imaging capability of the jPET-D4, a prototype brain PET scanner. The jPET-D4 consists of novel detectors which provide 4-layer depth-of-interaction (DOI) information of multi-layered thin crystals.

4.1. Research on Molecular Imaging of Cancer

Tsuneo Saga, Ph. D.
Director, Diagnostic Imaging Group

Outline of Research Career :

Dr. Saga received a Ph.D. from Kyoto University in 1991 for his investigations on cancer targeting of radiolabeled monoclonal antibodies. He continued his research on antibody targeting at National Institutes of Health (1991-1993) and at Kyoto University (1995-2006). In addition, for the last 9 years, he has been conducting clinical and basic research covering the wide area of cancer imaging. Since 2006, he has been the leader of the Diagnostic Imaging Group at NIRS ; this group works to further advance the basic and clinical research on molecular imaging of cancers.

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Objectives :

Diagnostic Imaging Group is conducting research on functional imaging of cancer by PET and other modalities. By using various cancer-specific probes, the characteristics of an individual cancer growth such as malignancy grade and responsiveness to treatment can be clarified. This information can be used for treatment planning and evaluation of therapeutic effect. Although several PET probes such as FDG and ^{11}C-methionine are now routinely available for clinical studies, development of new imaging probes is necessary for more comprehensive evaluation of cancers and to further contribute to the management of cancer patients.

The Clinical Diagnosis Team focuses on clinical research of functional cancer imaging and is aiming to contribute to the management of cancer patients including those considered for carbon ion radiotherapy conducted in the Hospital of the Research Center for Charged Particle Therapy. In addition to the clinical research using routine PET probes, such as FDG and ^{11}C-methionine, we are evaluating newly developed cancer-imaging probes, such as ^{18}F-fluorothymidine (FLT) and ^{62}Cu-ATSM, to determine their clinical usefulness in the characterization and early diagnosis of various cancers.

The Molecular Diagnosis Team conducts basic molecular imaging researches focusing on designing and evaluation of PET probes that capture and depict the changes of biomolecules specifically associated with cancers and other diseases to realize effective non-invasive diagnoses. We also develop novel in vivo reporter gene imaging systems to facilitate the establishment of new therapies such as gene therapy and regenerative therapy.

The Biomolecule Team focuses on the elucidation of genetic/molecular events occurring during carcinogenesis, searching for suitable targets of molecular imaging of cancers. By using functional screening of genes related to cell growth or radiation susceptibility, and proteome analysis of the blood and tissue samples of cancer patients, we select the genes and proteins specifically expressed in cancers. Through the exploration of the targets with high specificity, we are aiming for the development of novel molecular imaging methods which can non-invasively depict the characters of each cancer.

Progress in Research

1) Clinical studies on cancer imaging using various PET probes

We are conducting clinical PET research using FLT, a marker of cell proliferation, in the evaluation of effectiveness of carbon ion radiotherapy (CIRT) in lung and head & neck cancer patients in collaboration with the Research Center for Charged Particle Therapy. Preliminary data from less than 20 lung cancer patients showed that tumor uptake of FLT significantly decreased 3 months after CIRT (Fig. 5). However, we observed FLT uptake in the area of radiation pneumonitis, which made the post-treatment evaluation difficult. Longer follow-up of a larger number of patients is necessary to evaluate the relationship of tumor FLT uptake and the development of recurrence and/or metastasis.

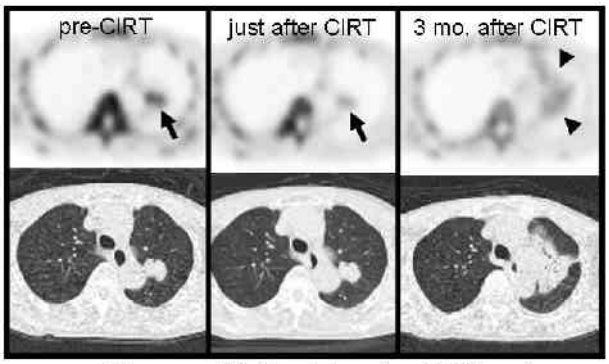

Fig.5 Change of FLT uptake after CIRT and the effect of radiation pneumonitis

Clinical investigation of PET with ^{62}Cu-ATSM, a marker of tumor hypoxia, has been ongoing as a multi-center study. In NIRS, ^{62}Cu-ATSM-PET is conducted for uterine cervical cancer patients in collaboration with the Research Center for Charged Particle Therapy. The uptake pattern of ^{62}Cu-ATSM varied from that of ^{11}C-methionine probably reflecting the difference in oxygenation pattern and amino acid metabolism within the tumor tissue. By comparing the treatment response with the uptake pattern of ^{62}Cu-ATSM for individual patients, we are expecting that ^{62}Cu-ATSM-PET can afford information on the selection of appropriate treatment strategy reflecting the grade of tumor hypoxia.

2) Loss of function screen identifies therapeutic and diagnostic potential targets in malignant mesothelioma

Malignant mesothelioma is a highly aggressive tumor arising from serosal surfaces of the pleura. Currently no single widely accepted treatment for mesothelioma results in a cure. To identify therapeutic and/or imaging molecular targets, we conducted a large-scale functional screening of mesothelioma cells using small interfering RNAs against 8,589 human genes. We determined that knockdown of 39 genes apparently suppressed mesothelioma cell proliferation. At least seven of these 39 genes would be involved in anti-apoptotic function. One of them was highly expressed in a sarcomatoid mesothelioma cell line, but not in normal mesothelial cells, epithelioid mesothelioma cells, and other tumor cells. This gene would be useful for developing effective therapeutic agents and a new diagnostic marker of sarcomatoid mesothelioma. Functional characterization of these genes identified by our screening should provide clues to the underlying new molecular mechanisms of apoptosis and potentiate the development of new therapy and diagnosis for malignant mesothelioma.

3) Investigation on novel targets of imaging by means of metabolome analysis

Metabolome analysis of various cultured cancer cell lines showed that cancer cells release more acetate into culture medium than normal cells do and that the acetate production in cancer cells further increased under hypoxic condition, which was not observed in normal cells. The up-regulation of acetate metabolism, both uptake and production, seemed to be mediated by the enzyme acetyl-CoA synthase 2 (Accs 2). The findings indicate that imaging with radiolabeled acetate is capturing tumor-specific and hypoxia-specific metabolism in cancerous tissue. We also identified a few more cancer cell-specific metabolites, which may lead to development of new tumor imaging PET tracers.

4) Development of animal models for the evaluation of imaging probes

To facilitate the evaluation of imaging probes, mesothelioma cell lines expressing red fluorescent proteins were established. In vivo optical imaging was performed for mice bearing heterotopic (subcutaneous) and orthotopic (pleural) transplants of red fluorescent mesothelioma cells, which gave positive images of the tumor. The models were proved to be useful to monitor tumor growth by measuring fluorescence intensity, while the response of tumor to chemotherapy was better monitored by PET tracer uptake. Among PET tracers tested, FLT seemed especially useful to monitor tumor response to pemetrexed which is approved for clinical use in combination with cisplatin for the treatment of mesothelioma.

5) Development of PET/SPECT tumor imaging using antibody probes

To image c-kit-positive tumors such as gastrointestinal stromal tumors (GIST), we labeled anti-c-kit monoclonal antibodies with ^{125}I and ^{111}In, and assessed their in vitro and in vivo characteristics (Fig. 6). According to cell binding, competitive inhibition and internalization assays in vitro, and biodistribution and SPECT imaging in vivo, the radiolabeled antibodies specifically bound to c-kit expressing cells and were internalized, and ^{111}In labeled antibody highly accumulated in xenografted tumors which were readily visualized by SPECT (Fig. 7).

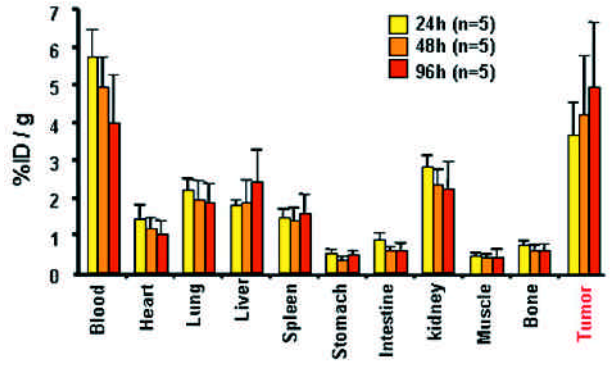

Fig.6 Distribution of ^{111}In anti-c-kit antibody

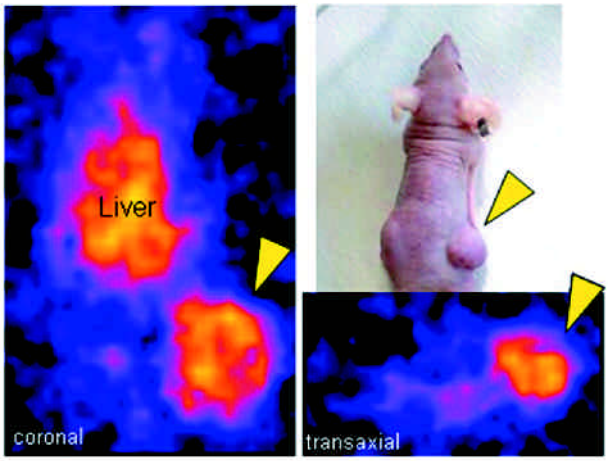

Fig.7 SPECT imaging

To image epithelioid mesothelioma, a radiolabeled monoclonal antibody recognizing mesothelioma related antigen (ERC/mesothelin) was assessed for its in vitro and in vivo characteristics. The radiolabeled antibody specifically bound to epithelioid mesothelioma cells and was internalized after binding, and ^{111}In labeled antibody highly accumulated in xenografted tumors which were readily visualized by SPECT.

6) PET imaging of malignant mesothelioma in model mice

Malignant pleural mesothelioma (MPM) is a highly aggressive tumor and the prognosis with current treatment remains poor. Thus, development of more effective treatments has been required. Noninvasive imaging is essential for assessment of the efficacy of new treatment. To establish noninvasive imaging for MPM, we compared tumor uptake of three PET tracers, ^{18}F-FDG, ^{18}F-FLT and ^{11}C-thiothymidine. We established subcutaneous and orthotopic models of epithelioid and sarcomatoid MPM in mice, and conducted biodistribution study and PET imaging. Two thymidine analogues, FLT and thiothymidine, were highly accumulated in epithelioid MPM, while glucose analogue, FDG, was highly accumulated in sarcomatoid MPM. Our results suggest that the suitable PET tracer is different for the evaluation of epithelioid and sarcomatoid MPM.

7) Development of novel reporter gene imaging

In order to develop a novel PET/MRI dual modality reporter gene imaging system, we are examining ferritin heavy chain (FHC) gene as a reporter. In vitro experiments demonstrated that cells transiently expressing FHC gene showed increased cellular uptake of iron resulting in the decreased T2 weighted (T2W) MR signal. When FHC gene was electroporated into mouse subcutaneous tumor, a localized region of lowered T2W signal was observed which coincided with the gene delivery.

8) Search for specific molecular target of asbestos-induced mesothelioma imaging through investigation of the mechanism of carcinogenesis

For the early detection of asbestos-induced mesothelioma, we investigated the mechanism of carcinogenesis associated with asbestos exposure. We found that exposure of normal mesothelial cells to asbestos caused the increased expression of ferritin heavy chain gene, and some mesothelioma cell lines had increased levels of FCH expression. Our study indicated that increased expression of FHC was involved in mesothelioma formation through decreasing the production of reactive oxygen species induced by asbestos exposure. It is proposed that the acquired resistance to apoptosis caused mesothelial cells to survive under additional carcinogenic stimuli which lead to mesothelioma formation.

We also found that the contents of other heavy metals, such as manganese (Mn) and copper (Cu), in various mesothelioma cell lines are increased compared to normal mesothelial cells, indicating the possibility that these heavy metals are involved in mesothelioma formation and/or progression.

9) Development of neovascularization and tumor imaging by PET

Tumor neovascularization is important not only in the local growth of tumors, but also in tumor invasion and metastasis. Integrin $\alpha_v\beta_3$ is expressed on the surface of endothelial cells of newly formed vessels in tumors and on some tumor cells themselves. Various analogs of RGD peptides bind to integrins and have been used for imaging tumor neovasculature. Among them, RAFT-c $(RGD)_4$ developed by Dr. Dumy containing 4 cyclic RGDs in a single molecule (RGD tetramer) is a very specific and high affinity ligand for integrin $\alpha_v\beta_3$, and fluorescence (cy5) -labeled RAFT-c $(RGD)_4$ successfully imaged integrin $\alpha_v\beta_3$ expressing tumors.

In collaboration with Dr. Dumy's group, we have synthesized cyclam conjugated RAFT-c $(RGD)_4$ and now are optimizing its labeling condition with positron emitting Cu isotopes for PET imaging.

10) Development of PET probes for EGFR imaging

EGFR (epidermal growth factor receptor) is often overexpressed and/or mutated in many cancer cells and its abnormal activation is implicated in carcinogenesis and cancer progression. There have been several pharmaceuticals developed for molecular targeting of EGFR. To characterize the cancer and aid treatment planning, we attempted to develop imaging probes to capture the activated state of EGFR. We designed a peptide probe binding to activated EGFR and are now validating the feasibility of the design.

Major Publications :

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2) Koizumi M, Koyama M, Tada K, Nishimura S, Miyagi Y, Makita M, Yoshimoto M, Iwase T, Horii R, Akiyama F, Saga T : The feasibility of sentinel node biopsy in the previously treated breast. Eur J Surg Oncol 34 : 365-8, 2008.
3) Sudo H, Tsuji AB, Sugyo A, Imai T, Saga T, Harada YN : A loss of function screen identifies nine new radiation susceptibility genes. Biochem Biophys Res Commun. 364 : 695-701, 2007.

4.2. Molecular Neuroimaging Research

Tetsuya Suhara, M.D., Ph.D.
Director, Molecular Neuroimaging Group

Outline of Research Career

Dr. Suhara began working at NIRS in 1989. He received the Ph.D. from Jikei University School of Medicine in 1991 for his study of dopamine receptor binding in vivo. In 1992-1993, he studied in the PET Group of the Department of Clinical Neuroscience, Karolinska Hospital, Sweden. He has had a long-time research interest in brain functional imaging. Since 2004, he has been a visiting professor in the Department of Neuropsychiatry, Nippon Medical School ; since 2006, he has held a similar position in the Graduate School of Medicine, Yokohama City University.

Contact point : suhara@nirs.go.jp

Objectives

1) Clinical Neuroimaging
   a) Development of quantitation and imaging methods of the noradrenalin transporter, NK1 receptor and dopamine synthesis.
   b) Construction of the database for normal functions of the serotonergic and dopaminergic neurotransmission systems.
   c) Investigation of the changes in the neurotransmission functions in schizophrenia and nicotine addictions.
   d) Pathological and therapeutic investigations in Alzheimer's disease (AD) and schizophrenia using PET.

2) Molecular Neurobiology
   a) Clarification of the correlation between abnormalities of the monoaminergic neurotransmission and behavior in murine models of psychiatric conditions, including calmodulin/calcium-dependent kinase II? knockout (CaMKIIα -KO) mice, for gaining insights into the molecular etiology of mental disorders.
   b) Establishment of in vivo imaging systems for genetically engineered mice in the search for pathology-based biomarkers applicable to the diagnosis and therapeutic evaluation of AD.
   c) Elucidation of roles of monoaminergic and glutamatergic receptors in the pathogenesis of drug-induced psychosis by means of combined imaging and electrophysiological assays.
   d) Pursuit of activated glia in experimental models using imaging biomarkers leading toward the development of diagnostic and therapeutic approaches to neuropsychiatric disorders.

3) System Neurochemistry
   a) Exploration of the differences in brain function between dopamine D1 and D2 receptors with awake monkeys well-trained in a sophisticated manner to further understanding of the neuropharmacological mechanism of anti-psychotic drugs and the pathophysiology of neuropsychiatric disorders.
   b) Functional specialization responsible for drug addiction and investigation of extrastriatal dopaminergic aberrant function in addicted monkeys using PET in the awake condition.

Progress of Research

1) Clinical Neuroimaging
   a) Non-invasive and simple methods for quantitation of noradrenalin transporter with [^{18}F] FMeNER and NK1 receptor with [^{18}F] FE-SPARQ could be established. The rapid calculation method for imaging of dopamine synthesis has been developed for [^{11}C] DOPA PET studies.

   b) The normal database of the serotonergic neurotransmission functions has been constructed and their in vivo distributions were clarified. By refinement of the normal database of dopaminergic neurotransmission functions, their distributions have been demonstrated to be in good agreement with those from human postmortem studies.

   c) A significant correlation has been shown between the binding potential of [^{11}C] Ro15-4513 to the central benzodiazepine receptors and the negative symptoms in patients with schizophrenia. An fMRI study of the schizophrenia delineated that the pattern of the transmission of inhibitory signals from insula to amygdala was different from normal signals. A PET study with [^{11}C] raclopride suggested that nicotine dependence in smokers

was related to the nicotine-induced dopamine release in the ventral striatum.

d) A PET study with [^{11}C] PIB demonstrated that the deposition of β-amyloid in the patients with mild cognitive impairment was observed in the parietal cortex and in AD patients it extended to the frontal and temporal cortices, excluding the sensorimotor area. No differences in dopamine D2 receptor occupancies with atypical antipsychotics olanzapine between the striatal and extrastriatal regions were shown in patients with schizophrenia.

2) Molecular Neurobiology

a) By visualization of monoaminergic dysfunctions in CaMKIIα-KO mice using microPET, we have established an *in vivo* biochemical monitoring technique that can be employed in conjunction with behavioral tests for longitudinal assessments of these animal models. This experimental system should be particularly powerful in the discovery of drugs targeting monoaminergic neurotransmissions and should be capable of counteracting behavioral phenotypes.

b) Comparative PET, autoradiographic and immunohistochemical assays for brains of human AD and transgenic mice modeling amyloid-β peptide (Aβ) pathologies in AD have revealed that the primary high-affinity binding sites for amyloid probes, as exemplified by [^{11}C] Pittsburgh Compound-B ([^{11}C] PIB), is composed of N-terminally cleaved and modified Aβ subspecies, Aβ N3 (pE), which would thus be a target molecule for the diagnosis and treatment of AD. Studies of these model mice have also demonstrated that therapeutic elimination of AD-like amyloid lesions and associated microglial activation following treatments with anti-Aβ antibodies can be quantified by microPET scans with [^{11}C] PIB and [^{18}F] fluoroethyl-DAA1106, respectively. In collaboration with Tohoku University, a new ^{18}F-labeled PET probe for amyloid imaging named [^{18}F] Fluorinated Amyloid-binding Compound of Tohoku University ([^{18}F] FACT) was characterized by a side-by-side comparison of [^{18}F] FACT and [^{11}C] PIB in model mice, proving the potential utility of [^{18}F] FACT in preclinical and clinical applications. We have also provided the first demonstration of in vivo visualization of neurofibrillary tau lesions, which are pathological hallmarks in AD along with Aβ amyloid, in tau transgenic mice; this was done with the aid of newly designed and/or screened imaging agents.

c) Modulation of the dopaminergic neurotransmission by glutamate receptors has been visualized in living monkeys and rats by using PET and an agonistic radioligand for dopamine D2 receptors, (R) -2-$^{11}CH_3$O-N-n-propylnorapomorphine ([^{11}C] MNPA). The mechanism of actions by which glutamatergic suppressions lead to a reversal of drug-induced dopaminergic overflows was further clarified by obtaining electrophysiological data linkable to the [^{11}C] MNPA-PET results.

d) The peripheral benzodiazepine receptors (PBR) were demonstrated to be expressed in not only microglia but also astrocytes during the time course of toxicant-provoked brain injuries. Subsequent analyses of PBR in animal models of diverse neurological conditions have indicated mechanistic relationships between astrocytic PBR and neurotrophic/neuroprotective supports by activated glia, providing implications of the PBR imaging for therapeutic evaluations of neuroglial pathologies.

3) System Neurochemistry

a) In normal rhesus monkeys, the spatial differences of the brain in distributions of dopamine D1 and D2 receptors are consistent and the quantitation of PET data in some brain regions is unlikely to be reliable. Parkinson's disease model with monkeys showed the reduction in binding potentials of D1 and D2 receptors in extrastriatal regions, such as the frontal (lateral and medial), parietal and temporal cortices and the thalamus.

b) Iin collaboration with Juntendo University, we obtained monkey PET results, focusing on the information processing of temporal order judgment (TOJ). The results identified the regional activation in the brain when the monkey had to make a decision of temporal order for serial tactile stimuli presented at its both its hands in a sequential manner. To validate the causal relationship between rCBF increase and neurons residing at one of the activated area (secondary somatosensory area II ; SII) , we investigated the effect of local inactivation of SII by muscimol, $GABA_A$ agonist, on TOJ performance, in conjunction with a unit recording of neuronal mapping.

c) Drug addiction is characterized by psychic dependence, namely constant uncontrollable craving for drugs. It is well known that as an animal model, drug addiction (psychic dependence) can be represented by intravenous self-administration of the drug, especially with a progressive ratio (PR) schedule of reinforcement, in which the number of lever presses required on each consecutive run is increased by a fixed gain. We

are examining in vivo functional substrates underlying the psychic dependence on cocaine by measuring regional cerebral blood flow (rCBF) using PET with O-15 labeled water when macaques were performing intravenous self-administration of cocaine on a PR schedule. Our PET results have shown increases of rCBF in dorsolateral prefrontal cortex (PFC), orbitofrontal cortex, anterior cingulate cortex, nucleus accumbens (NAc), striatum, thalamus, and ventral tegmental area (VTA) in the cocaine reinforcement condition, relative to a food (banana-flavored pellet) reinforcement condition as control. These findings are consistent with reports from a series of in vitro studies showing plasticity, starting with LTP in VTA, NAc to PFC. Therefore, PET measurements may be very useful for demonstrating in vivo functional organization responsible for drug addiction. As well, our preliminary results suggest that the binding potentials of D1 and D2 are likely to decrease in the anterior cingulate and frontal cortices and the thalamus after cocaine addiction.

Major Publications

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3. Ito H, Takahashi H, Arakawa R, Takano H, Suhara T : Normal database of dopaminergic neurotransmission system in human brain measured by positron emission tomography. NeuroImage 39 : 555-565, 2008
4. Asai Y, Takano A, Ito H, Okubo Y, Matsuura M, Otsuka A, Takahashi H, Ando T, Ito S, Arakawa R, Asai K, Suhara T : GABAA benzodiazepine receptor binding in patients with schizophrenia using [^{11}C] Ro15-4513, a radioligand with relatively high affinity for α5. Schiozophr Res 99 : 333-340, 2008
5. Takahashi H, Fujimura Y, Hayashi M, Takano H, Kato M, Okubo Y, Ito H, Suhara T : Enhanced dopamine release by nicotine in cigarette smokers. Int J Neuropsychopharmacol 39 : 483-491, 2008

4.3. Studies on Molecular Probes and Radiopharmaceuticals

Kazutoshi Suzuki, Ph.D.
Director, Molecular Probe Group

Objectives

Molecular probes play essentially important roles in the rapidly developing molecular imaging field. The purposes of the Molecular Probe Group are: 1) developing novel probes assessing in vivo biological and physiological functions (Probe Research Team); 2) developing a new labeling method to expand the possibility of producing a wider variety of probes at high yield and high quality (Radiochemistry Team); 3) developing a new integrated system for the production of safe probes considering the GMP standard, without radiation exposure to personnel by automation (Production System Team); and 4) establishing production methods and quality control methods of developed probes for clinical applications (Radiopharmaceutical Production Team).

The Probe Research Team has objectives to develop novel probes for quantitative assessment of oxidative stress and/or disruption of homeostasis and brain efflux function targeting multidrug resistance-associated protein (MRP). This team also takes part in the development of novel tumor imaging probes to assess DNA synthesis in tumor cell proliferation and in the development of novel receptor ligands. The Radiochemistry Team has objectives to develop new labeling methods with PET radionuclides; in particular, the team is working on a direct fluorination method for 18F- to a benzene ring and to achieve higher specific activity for various kinds of PET probes. The Production System Team and Radiopharmaceutical Production Team have not only the above objectives but also missions to support research activities for PET molecular imaging in collaboration with the Planning and Promotion Unit. The research activities of FY2007 are summarized below.

Progress in Research

1) Probe Research Team

We have addressed the development of novel probes to assess in vivo biological and physiological functions by talking approaches with a rationale-based design, as well as modification of potent probes. Our targets are molecules and/or functions involved in bio-defense systems, judgment of malignancy and a therapeutic response in tumors, and neurotransmission. The following studies were carried out.

In the research on probes assessing oxidative stress and/or disruption of homeostasis, two subjects have been investigated. A probe study was launched to assess glutathione S-transferase activity, a key enzyme related to GSH maintenance, in the brain. A series of compounds were designed based on a metabolic trapping principle and their reactivity with GSH was examined to evaluate properties as a probe. Another probe study focused on quantitative assessment of brain efflux function. Targeting multidrug resistance-associated protein (MRP), we designed 6-halo-purine derivatives were designed on the basis of a metabolite extrusion method and some of them were found to be promising.

A novel thymidine analog, 4'- [methyl-^{14}C] thiothymidine ([^{14}C] S-dThd), was further evaluated to assess DNA synthesis in tumor cell proliferation. The result provided us with evidence that [^{14}C] S-dThd is a promising marker for DNA synthesis.

In collaboration with a clinical-research group, we investigated ^{11}C-MP4A/PET (for AChE) and ^{11}C-PIB/PET (for amyloid) for application to diseases with dementia symptoms.

2) Radiochemistry Team

a) Labeling Technique

A practical route for preparing [^{18}F] ligand containing [^{18}F] fluorobenzene moiety was developed

by employing a reaction of diphenyliodonium salt with [^{18}F] F$^-$. Using this method, [^{18}F] FDOPA, a PET radiopharmaceutical for the imaging of dopaminergic presynaptic function, was synthesized in a high yield (20-30% radiochemical yield based on ^{18}F$^-$) and high specific activity (1Ci/μmol).

we prepared [^{11}C] acetyl chloride ([^{11}C] AcCl) in a loop method by reacting methylmagnesium bromide with [^{11}C] CO_2, followed by treatment with oxalyl choride. [^{11}C] AcCl was applied for the preparation of [^{11}C] oseltamivir and its activated form ([^{11}C] Ro64-0802), which are. After reaction, [^{11}C] AcCl was purified by distillation as a radiochemically pure product and it could be used for high efficiency acylation for nucleophilic substrates such as phenol and amine.

A new labeling method generating ^{11}C-C bond was developed by using [^{11}C] nitromethane. C-carboxylation of [^{11}C]nitromethane was accomplished from [^{11}C] methyl nitronate and 1-ethoxycarbony-lbenzotriazole to afford [2-^{11}C] ethyl nitroacetate in a radiochemical yield of 75±6%. [2-^{11}C] Glycine ethyl ester was synthesized as a simple application of [2-^{11}C] ethyl nitroacetate.

b) Specific activity

In vitro binding of [^{11}C] raclopride with ultra-high specific activity (SA) in the striatum and cerebral cortex of rat brain was characterized. The ***in vitro*** homogenate assay demonstrated that high SA [^{11}C] raclopride (>2500 GBq/μmol) had two affinity binding sites in the striatum and cerebral cortex of rat brain. By contrast, using low SA [^{11}C] raclopride (44 GBq/μmol), only one binding site was found in the striatum and no binding site was identified in the cerebral cortex.

c) Novel PET ligand

[^{11}C] AC-5216 was synthesized and evaluated as a PET ligand for imaging PBR in primate brain. A PET study on the monkey brain determined that [^{11}C] AC-5216 had relatively high uptake in the occipital cortex which is known as a rich PBR dense area in the primate brain. Pretreatment with non-radioactive AC-5216 and PK11195 reduced the radioactivity of [^{11}C] AC-5216 in the occipital cortex significantly, suggesting it had highly specific binding with PBR in the brain.

3) Radiopharmaceutical Production Team

A highly sensitive microdialysis-radio-LC system was developed and evaluated for the metabolite analysis of PET radiopharmaceuticals in a rat brain. This system made it possible to determine the metabolites of the PET probes automatically in a small animal brain with extremely high sensitivity (2 Bq), high-resolution, and high-throughput.

The team supported research conducted in the Molecular Imaging Center and HIMAC and the production and quality control of short-lived PET radiopharmaceuticals was carried out for both for clinical and animal experiments. Four new PET radiopharmaceuticals ([^{11}C] MNPA, [^{11}C] AC5216, [^{11}C] Gefinitib, and [^{18}F] -labeled compound for β-Amyloid imaging) were approved for the clinical use by the Institutional Review Board at NIRS.

The contracts for the analysis of FDG solutions were made with four private companies. Under the contracts, 216 samples from 86 PET facilities in Japan were accepted for analysis.

Major Publications

1) T. Okamura, T. Kikuchi, K. Fukushi, Y. Arano, T. Irie : A novel noninvasive method for assessing glutathione-conjugate efflux systems in the brain, Bioorganic & Medicinal Chemistry, 15 (9), 3127-3133, 2007

2) R. Nakao, K. Furutsuka, M. Yamaguchi, K. Suzuki: Quality control of PET radiopharmaceuticals using HPLC with electrochemical detection, Nuclear Medicine and Biology, 33 (3), 441-447, 2006

3) M. Zhang, K. Suzuki: [^{18}F] Fluoroalkyl Agents: Synthesis, Reactivity and Application for Development of PET Ligands in Molecular Imaging, Current Topics in Medicinal Chemistry, 7 (18), 1817-1828, 2007

4) M. Zhang, K. Kumata, K. Suzuki : A practical route for synthesizing a PET ligand containing [^{18}F] fluorobenzene using reaction of diphenyliodonium salt with [^{18}F] F-, Tetrahedron Letters, 48 (49), 8632-8635, 2007

5) J. Noguchi, M. Zhang, K. Yanamoto, R. Nakao, K. Suzuki : In vitro binding of [^{11}C] raclopride with ultrahigh specific activity in rat brain determined by homogenate assay and autoradiography., Nuclear Medicine and Biology, 35 (1), 19-27, 2008

4.4. Research and Development of the Next-generation Technology for Molecular Imaging

Iwao Kanno, Ph.D.
Director, Biophysics Group

Outline of research career

Iwao Kanno started his professional career at Akita Research Institute of Brain and Blood Vessels in 1970, where he was an active researcher for 36 years. In 1977, he developed a custom radionuclide emission tomography system using a handmade rotational dentist chair. In 1979 in collaboration with Shimadzu, he developed a hybrid type of emission tomography which combined positron emission tomography (PET) and single photon emission computed tomography (SPECT). His efforts were also directed to developing methodology for quantitative assessment of physiological and biochemical parameters from PET and SPECT images.

Objectives

The Biophysics Group works to develop methodologies and technologies for watching, detecting, analyzing and understanding the molecular and physiological signals emitted from humans and the living animals. This is done by using the kinetics of radioactive molecular probes, magnetic resonances signals of protons interacting with molecular probes, multi-photon laser microscopy and engineering physics for detection and imaging of positron annihilations. The group consists of four research teams. The Imaging Physics Team covers software and engineering physics involved in PET instrument systems. The Biosignal Physiology Team combines molecular information and physiological information measured from MRI and the microcirculation facilities on hemodynamic signals relating to neurovascular coupling during neuronal activation. The Data Analysis Team aims to extract quantitative parameters from dynamic PET images taken from patients and healthy subjects after radioactive ligand administrations. The Magnetic Resonance Molecular Imaging Team develops methods for detecting the variable signals from the high tesla (7T) MRI. These four teams collaborate to assess quantitative molecular mechanisms from in vivo measurements on humans and other animals. The Biophysics Group is thus supporting research and applications of other groups working on molecular diagnostic imaging and molecular neuropsychiatric imaging at the Molecular Imaging Center.

Progress of Research

1) Magnetic Resonance Molecular Imaging Team

a) Immunocyte labeling and tracking

Non-invasive in vivo detection of transplanted cells is an important technique for regenerative biology and medicine. We developed a new nontoxic method for labeling immunocytes that provides MRI signal enhancement. The labeled immunocytes were intramuscularly administered to a rat ischemic leg and heart model and imaged with the 7T MRI.

b) Quantum-dots

Multimodal probes were developed from quantum-dot nanoparticles for both MR and optical imaging. Quantum-dots have higher fluorescence properties than conventional organic dyes. The fluorescence properties were protected by using a hydrophobic structure around the nanoparticle core and MRI contrast agents were facilitated by adding a further amphiphilic silica shell structure.

c) Reactive gliosis

Reactive gliosis is an important neuronal response after stroke or spinal cord injury. Recently, it has been a subject of interest in regenerative medicine. We proved that a manganese MRI contrast agent can provide good image contrast for studying reactive gliosis in a rat stroke model.

d) Macaque brain anatomy

The Macaque monkey has a similar brain structure to humans so that its embryology can provide useful information for human neuroembryology as an example of "translational research". MRI can provide non-destructive and 3D anatomical mapping including molecular/cellular information. We developed a method for making stable MRI measurements using high field MRI and we traced embryo development in the macaque brain exvivo.

e) Mouse spinal cord

Visualization of spinal cord is needed not only for injury treatment but also for transplantation and regeneration therapy/research. Although there are many useful transgenic mouse models, the mouse spinal cord is difficult to visualize by MRI because of the small size (under 1 mm^2). We developed a two

channel phased array coil for mouse spinal cord and obtained images with in-plane resolution of less than 75 μm.

f) Drug delivery imaging

We tested the possibility of liposomal drug delivery imaging in vivo. The liposomes can contain both MRI contrast agent and anti-cancer drugs. They are a good candidate for achieving molecular/cellular MR imaging using a drug delivery technique.

g) Diffusion and functional imaging

We prepared the environment and methods necessary for detecting functional and diffusion MRI in animals. High quality images successfully obtained of rat brain at high diffusion-weighting (b=5000 s/mm^2) with and without the injection of a USPIO contrast agent. Preliminary tests were done for functional imaging using a somatosensory stimulation model, and we successfully obtained an acceptable response.

h) RF coil development

When imaging a human body using an ultra-high magnetic field MRI system (a magnetic flux density 7 T or more), artifacts may be caused by the influence of the dielectric effect etc. induced by the shortness of the wavelength. It is difficult to create a big volume coil because the target wavelength is short. To overcome these problems, we developed a Patch Antenna Array Coil (PAAC), which is a coil configured as a combination of patch antennas. We prototyped this type of coil for 7 T proton MRI, imaged a monkey brain, and confirmed that it is usable as an RF coil for ultra-high field MRI.

2) Biosignal Physiology Team

a) Diffusion functional MRI

Recently, it has been suggested that diffusion-weighted fMRI could provide a more direct method of observing neuronal activity. Signala originated from the brain during hypercapnia and visual stimulation diffusion-weighted fMRI experiments were decomposed into intravascular, fast-diffusion phase, and slow-diffusion phase components. It was concluded that the slow-diffusion phase signal change must reflect neural activation, although the exact mechanism remains unclear.

b) GSH-edited 1H MRS for schizophrenia

Glutathione (GSH), a major intracellular antioxidant, plays a role in NMDA receptor-mediated neurotransmission, which is involved in the pathophysiology of schizophrenia. We wanted to investigate whether GSH levels are altered in the posterior medial frontal cortex of schizophrenic patients. Twenty schizophrenia patients and 16 age- and gender-matched normal controls were enrolled to examine the levels of GSH using 3T 1H-MRS with the spectral editing technique, MEGA-PRESS. Clinical variables of patients were assessed by the Scale for the Assessment of Negative Symptoms (SANS). There was a significant negative correlation between GSH levels and the severity of negative symptoms (SANS total score and negative symptom subscore) in schizophrenic patients, suggesting that GSH levels in the posterior medial frontal cortex may be related to negative symptoms in them. Therefore, agents that increase GSH levels in the brain could be potential therapeutic drugs for negative symptoms in schizophrenia.

c) New diffusion tensor parameter for cancer diagnosis

The apparent diffusion coefficient (ADC) provides the possibility of adding information for an accurate diagnosis of prostate cancer. The ADC use only eigenvalues from the DTI information. It is suspected that the structure will show deformities if prostate cancer exists. Eigenvectors of the DTI might be applicable to estimate tissue structures. We propose a quantitative evaluation method, the inner product of intervoxel eigenvector (IPIE) method, to assess structural tissue changes from eigenvectors. The IPIE values in the prostate cancer region are significantly changed before and after carbon ion radiotherapy. These results suggest the IPIE method can quantitatively evaluate changes of tissue structure.

d) Direct visualization with fluorescent microscopy

An area (5 mm x 7 mm) on the rat left parietal bone was thinned. For visualization of cortical vasculature, a bolus of Qdot605 (1μM) was intravenously injected (0.2 to 0.4 ml), and three-dimensional vascular structure was visualized with in vivo multi-photon excitation fluorescent microscopy (TCS SP5, Leica Microsysems CMS GmbH). The region of interest (0.9 mm × 0.9 mm square) was determined, and was centered at 1.0 ± 0.4 mm caudally and 2.6 ± 0.5 mm laterally from the Bregma (Mean ± SD, N = 5), thus avoiding a relatively large pial vessel area in the primary somatosensory cortex. The vein emerging from the parenchyma was identified by tracking the pial venous networks, and its cross-sectional diameter was measured at the focal point. Three-dimensional vascular images were obtained from the cortical surface to a depth of 0.9 mm with a 0.01-mm z-step. The number density and cross-sectional diameter of veins continuing from the pial networks to the parenchyma were measured at a depth of 0.4 mm.

e) Number density and cross-section diameter of emerging veins with fluorescent microscopy

Cross-sectional images of emerging veins were clearly observed from the cortical surface up to a 0.5

mm depth under our experimental conditions. Most of the capillary networks could be continuously tracked from the branching of penetrating arterioles to veins. However, some vessels hiding behind the large pial veins were not completely visualized. In this study, we focused on the number of veins diving from the pial venous networks to the parenchyma up to a depth of 0.4 mm. The mean of the cross-sectional diameter was 17 ± 10 μm (n = 59 veins, N = 5 animals) and the number density was 13 ± 4 numbers per mm2 at a depth of 0.4 mm. The histogram showed a dense distribution of relatively small sized veins compared to a sparse distribution of large sized veins.

3) Image Analysis Team

This team aims to realize algorithms to measure and visualize various functionalities of humans and animals using PET. For fully quantitative PET molecular imaging, a parametric model analysis based on kinetics of an administered radiopharmaceutical in tissues is conducted. In a practical situation, large noise in the PET data is problematic. To realize PET functional imaging, mathematical and image processing techniques should be adopted. We developed and evaluated some new algorithms : omission of arterial blood sampling using an intersectional searching algorithm and clustering and a denoising algorithm for voxel-based model estimation using Wavelet transformation. Moreover, a quantitative PET scan for mice is important for molecular imaging investigations because of the large variety of genetically modified mice. The parametric analysis requires some radioactivity be introduced into the arterial blood. However, this is difficult to do because of the small size of the mice. The team is investigating surgical methods to insert a small catheter into a mouse artery and a system for arterial sampling.

4) Imaging Physics Team

This team demonstrated the imaging capability of the jPET-D4, a prototype brain PET scanner. The jPET-D4 consists of novel detectors which provide 4-layer depth-of-interaction (DOI) information of multi-layered thin crystals . Initial evaluation results showed that the jPET-D4 had almost uniform spatial resolution of around 3mm and more than 11% sensitivity for a centered point source with a standard 400keV - 600keV energy window. In order to compare the jPET-D4 with a commercial PET scanner, six healthy volunteers were scanned by the ECAT EXACT HR+ and the jPET-D4. Detailed analysis of this is now underway. The technology for discriminating 4-layer DOI information was applied to a higher resolution DOI detector for small animal imaging .

It has been pointed out that the long patient port of the state-of-the-art PET scanners such as the jPET-D4 tends to put stress on patients. Therefore we proposed an OpenPET geometry, which consists of two axially separated detector rings (Fig. 8). We have shown a number of points. First, a long and continuous FOV including a 360-degree open gap between two detector rings can be imaged, allowing a fully 3D image reconstruction of all the possible lines-of-response (LORs). Second, OpenPET is practical when iterative image reconstruction methods are applied even though image reconstruction of OpenPET is analytically an incomplete problem. Third, we see that axial spatial resolution, which is degraded with the extended gap due to the parallax error, can be recovered by utilizing DOI detectors.

In order to evaluate imaging performance of the proposed open PET geometry, we simulated a dual scanner (ring diameter of D=827 mm, axial length of W=154 mm x2) separated by a variable gap. The gap W was the maximum limit to have axially continuous FOV of 3W though the maximum diameter of FOV at the central slice was limited to D/2. We also tested the open PET geometry using experimental data obtained by the jPET-D4. The jPET-D4 has 5 rings of 24 detector blocks. We simulated the open jPET-D4 with a gap of 66 mm by eliminating 1 block-ring from experimental data. Although some artifacts were seen at both ends of the opened gap, very similar images were obtained with and without the gap. The proposed open PET geometry is expected to lead to realization of in-beam PET, which is a method for an in situ monitoring of charged particle therapy, by letting the beams pass through the gap. The proposed open PET geometry will also allow simultaneous PET/CT measurements of the same PET FOV as the CT FOV, in contrast to the conventional PET/CT where each FOV is separated by several tens of centimeters.

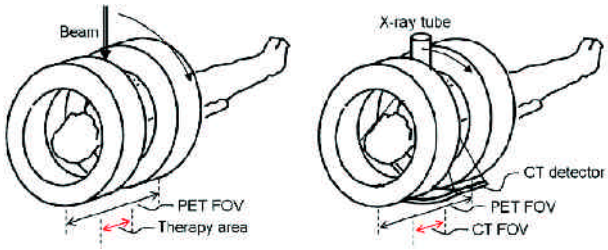

Fig. 8. Proposed OpenPET geometry applied for in-beam PET (left) and for simultaneous PET/CT (right).

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(Biosignal Physiology Team)
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5. Research Center for Radiation Protection

Kazuo Sakai, Ph.D.,
Director, Research Center of Radiation Protection

Outline of Research Career :

In 1982, Dr. Sakai got a Ph. D. degree in biochemistry from the University of Tokyo. He first worked as a Research Associate in the Department of Radiation Biophysics, Faculty of Medicine, University of Tokyo (1982-1989), and then as a Lecturer in the Department of Radiation Oncology, Graduate School of Medicine, University of Tokyo (1989-1999). The main subjects of his research were radiation induced DNA damage and its repair, and mechanism of radiation induced cell death. From 1983 to 1985 he worked as a research fellow in the Genetics Division, Children's Hospital, Harvard Medical School. At that time, his research subjects were gene amplification and cloning of genes responsible for radiosensitivity. He joined the Central Research Institute of Electric Power Industry in 1999 to research biological effects of low dose radiation. He has been at NIRS since 2006.

Objectives

The Research Center for Radiation Protection was newly established in 2006. The aim of the Center is to provide a scientific basis for radiation protection and safety. Toward this goal, radiation exposure from various sources is measured, the dose-effect relationships for various endpoints are examined, and the mechanisms underlying the effects are investigated. The Research Center disseminates its research results to promote public understanding of radiation effects and to encourage the enactment of more reasonable regulations concerning the use of radiation. The scope of its activity is not limited to Japan. It has been appointed a Collaborating Centre by the International Atomic Energy Agency.

Overviews

The Research Center consists of four research groups (Regulatory Sciences Research Group, Experimental Radiobiology for Children's Health Research Group, Radiation Effect Mechanisms Research Group, and Environmental Radiation Effects Research Group), Nakaminato Laboratory for Radioecology, and the Department of Advanced Technologies for Radiation Protection Research.

The activities of the research groups and the Nakaminato Laboratory are described in their respective sections. The Department of Advanced Technologies for Radiation Protection Research consists of four sections. Their activities in FY2007 are summarized below.

The Advanced Analytical Technology Section carried out cooperative projects with other research groups from inside and outside of NIRS to measure trace elements in environmental and biological samples. Also, the research work to clarify the effects of rhenium concentration on environmental Tc-99 analysis was finalized. Two research papers were published on the development of Re and U determination methods.

The Animal Pathology Section provided histopathology technical and diagnostic supports for NIRS intramural research projects.

The Advanced Animal Research Section supported integrated research of molecular and genetic studies with physiological studies in whole animals. Although remarkable progress of radiation biology has been made in genetic, molecular and cellular levels, physiological analysis of whole animal models is necessary for extrapolation to human health. The section supported radiobiological research by application of assisted reproductive technologies (ARTs) in genetically modified laboratory mice, including in vitro fertilization, embryo transfer, micromanipulation of embryos and cryopreservation. Such technologies have also become essential to efficiently conduct large scale animal experiments by providing a large number of animals synchronously.

The Environmental Radioactivity Survey Section initiated three collaborative research projects with three Japanese universities. They involve development of an ultra sensitive radon decay products measuring system, establishment of a calibration procedure for radon and its decay products concentrations and development of a new technique (based on detection of Cherenkov radiation) for radon measurements. In addition to them, other six commissioned works were given to this section using NIRS technologies and facilities.

In the Research Center 58 permanent and 91 temporary members actively conducted their research. They produced 82 original papers ; in 70 papers, the researchers were the principal contributors and 12, they were supportive. The Center held a symposium on environmental effects of ionizing radiation. Also, the Center organized an International Workshop on the Biological Effects of Low Dose Radiation.

5.1. Regulatory Sciences Research for Radiation Safety and Protection

Hidenori Yonehara, Ph. D.
Director, Regulatory Sciences Research Group

Outline of Research Career

Dr. Yonehara received a Ph.D. from Shiga University of Medical Science in 1995 for his study on issue of risk from exposure to residential radon. He joined to NIRS in 1996 and began working on the studies related to dose evaluation from environmental radiation. From 2003 to 2006 he worked on development of radiation safety standards as Director for Radiation Protection Policy in Ministry of Education, Culture, Sports, Science and Technology (MEXT). Since returning to NIRS, he has studied dose evaluation from natural radiation sources as well as issues related to radiation safety regulation. Since March 2007, he has been working as Director of the Regulatory Sciences Research Group.

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Objectives

"Regulatory science" can be considered to be an integrated science of uniting views of rationality in science and society. The main objectives of regulatory sciences research for radiation safety and protection are to summarize scientifically based information for radiation safety regulation and to exchange information among different stakeholders to bridge the gap between science and society. The research programs of the Regulatory Science Research Group are focused on four points.

1) Summarizing radiation protection issues

The group aims to summarize achievements of research on radiation protection provided by NIRS, as well as universities and other research institutes in order to contribute to activities of relevant international organizations such as UNSCEAR, IAEA, OECD/NEA, and ICRP. The group also summarizes the information on radiation protection for dissemination to regulatory authorities and the public. To share the information with scientific organizations, regulatory authorities and the public, the group has constructed a research information network.

2) Construction of information databases for radiation risk assessment

The group constructs information databases on risk assessment for people who are exposed to low dose radiation and controllable natural radiation sources. Scientific information on radiological archives of experimental research, and on the exposures and health effects of radiation among different human populations, and on environmental effects of radiation from the epidemiological studies are collected for the databases.

3) Development of mathematical models

Using the results of basic research related to the radiation effects on health and environment, the group develops mathematical models for risk evaluation of health effects due to exposure to controllable natural radiation sources and due to medical exposure. The group also develops models for analysis of radiological effects on the environment.

4) Development of method for risk communication

The group collects case examples in which risk information on radiation safety is passed on to the public, and the group analyzes social psychology findings.

Progress of Research

1) Construction of information databases for radiation risk assessment

The scientific achievements related to radiation effects are to be summarized comprehensively in the UNSCEAR report. The group, together with an expert panel in Japan made a great contribution to UNSCEAR activities submitting the relevant data as well as scientific comments on the draft of the UNSCEAR report. The group also took part in summarizing the comments from experts in various fields for drafting the 2007 Recommendations of ICRP. The information on status for exposure due to industrial use of naturally occurring radioactive materials (NORM) was summarized and an integrated database with the information was constructed for workers in affected industries and for consumers of the products as well as researchers. Specific radioactivities of various samples of ores and stones for industrial or building materials were determined experimentally to make up for the lack of relevant data in the database. A method for studying on possible health effects associated with medical exposures during childhood was examined. Experimental results of long term animal exposure experiments were collected and archived in electronic format. Finally, an international workshop was carried out to discuss further research applications within the scope of radiation protection.

2) Study on mathematical models

The group aims to develop two types of mathematical models for regulatory science. The first is a model for simulation of carcinogenesis. The main purpose of studies using this model is to evaluate the radiation risk at low dose exposure. The second type of model is for evaluation of the effects of ionizing radiation on environmental biota and ecosystems, and the effects of other environmental toxicants. In order to study the interactions in a model aquatic microcosm, an individual-based computer simulation model was developed. The microcosm studied consisted of Euglena gracilis as an autotroph algae, Tetrahymena thermophila as a heterotroph protozoa and Escherichia coli as a saprotroph bacteria. There is a strong interaction between Tetrachymena and E. coli as the first is a predator of the second. Ecological toxicity tests were conducted to test the population level impacts of the biological effects of radiation and toxicants on the lethality and mobility factors that influence directly or indirectly influence growth and reproduction. Radiological effects on lethality of E. coli individuals were translated to the reduction of the equilibrium population of Tetrahymena. A synergistic effect was also observed by the simulation at the community level in the case of combined exposure of radiation and a toxicant which reduced the feeding efficiency of Tetrahymena (Fig. 9).

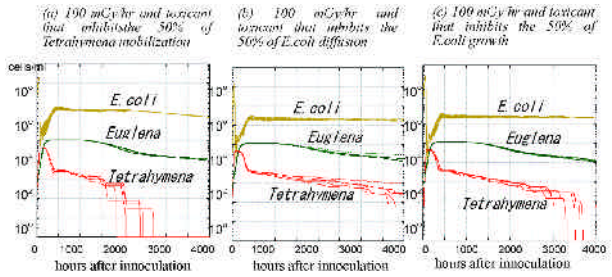

Fig. 9. Population level responses to the combined effects of chronic exposures of gamma radiation and toxicants simulated by SIM-COSM. Fig. (a), (b) and (c) show the combined effects on populations caused by exposures to gamma radiation (100 mGy/h) and toxicants that inhibit 50% of Tetrahymena mobilization, E. coli diffusion and E. coli growth, respectively.

3) Epidemiological study

An epidemiological study on lung cancer associated with residential radon in China is continuing. Recently, several pooled analyses of residential radon studies have indicated an increased risk of lung cancer even at the low radon level. Such consolidated analytical attempts, however, include data from several studies with different measuring methods and devices which are subject to large uncertainties associated with different measurement protocols. One of the most important factors in the measurements for epidemiological studies which should be taken into account is the issue of thoron (^{220}Rn). The results of measurements are likely to be affected by properties of detectors, especially their thoron sensitivity. Thoron concentrations can lead to overestimation of radon concentration and then to underestimation of lung cancer risk if measurement devices with high thoron sensitivity are used without discriminating it. On the other hand, not only radon but also existence of thoron is important itself. Although measurements of thoron gas provide nonessential information for occupant exposure assessment because of its short half-life (55.6 s) which means it cannot become uniform in room air, those of thoron decay products provide important dose information. Unfortunately, no common measurement protocol for thoron decay products or for radon has been established yet. Another important factor related to the measurements is an issue of retrospective radon measurement. Current concentrations of radon do not necessarily represent cumulative exposures to radon in the long term because there are large temporal and spatial variations in radon concentrations. We initiated a case-control study focused on thoron existence and historical radon exposure assessment in a rural area of Gansu Province, China. In our study, newly developed devices are employed for measuring both radon and thoron gases discriminatively, thoron decay products, and cumulative exposures to radon. The survey will be continued until 2009. Before conducting the main study, a pilot study was carried out from October 2006 to April 2007.

4) Study on biodosimetry

We studied the chemical induction of premature condensed chromosomes in human peripheral lymphocytes after culturing for 6 h. Many other researchers have attempted this induction without culturing or with short-term culturing, because this technique permits prompt cytogenetic biodosimetry of radiation accidents. Lymphocytes were separated from blood, incubated in the presence of phytohemagglutinin, ATP, and p34^{cdc2}/cyclin B kinase, and then treated with calyculin A during the last hour. The culture medium was supplemented with a lower concentration of fetal calf serum than conventionally used to minimize its possible interference with the effects of these drugs. We obtained, rarely, a suitable morphology of premature chromosome condensation in short-term cultured lymphocytes for conventional chromosome aberration analysis (Fig. 10).

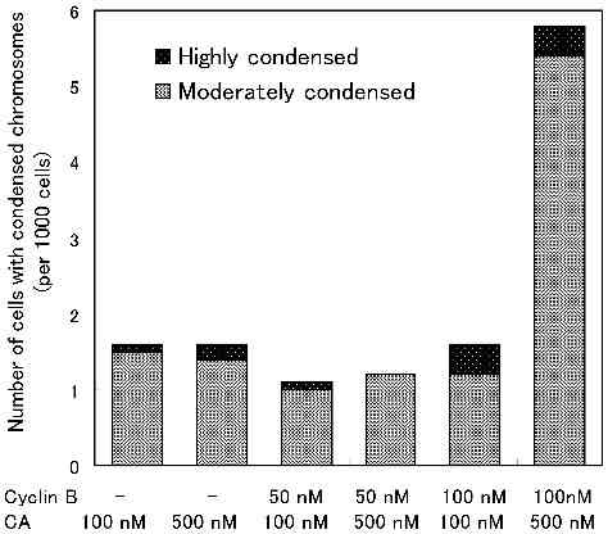

Fig. 10. Effects of p34cdc2/cyclin B kinase (Cyclin B) and CalyculinA (CA) on the frequency of cells with highly or moderately condensed chromosomes. Lymphocytes were cultured for 6 h in the presence of (2%) phytohemagglutin, 0.1 mM ATP, 0, 50, 100 enzyme unit/ml Cyclin B and 0.05 μg/ml colcemid and treated with 100 or 500 nM CA during the last hour. Frequencies are expressed as the numbers of cells having condensed chromosomes per 1000 cells plated into a culture tube.

5) Development of method for risk communication

We held a "Dialogue seminar" for risk communications among experts for NORM, users of industrial NORM and regulators. Fundamental information on NORM and an introduction to the NORM database developed by our group were illustrated by experts and issues related to NORM were discussed among stakeholders.

Major publications

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5.2. Experimental Radiobiology for Children's Health Research Group

Yoshiya Shimada, Ph.D.
Director, Experimental Radiobiology for Children's Health Research Group

Outline of Research Career

Dr. Shimada received a Ph.D. in 1985 from the University of Tokyo. At the Mizuno Biohoronics Project of JST (1985-1987) and at the Tokyo Metropolitan Institute of Gerontology (1987-1989), he worked on innate immunity in carcinogenesis and aging, respectively. Since 1989 at NIRS, he has focused on molecular and cellular mechanisms of T-cell lymphomagenesis and mammary carcinogenesis from the viewpoint of combined effect of environmental carcinogens and the age-at-exposure effect.

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Objectives

With the advent of an era of low birthrate and longevity, concerns about the safety of fetuses and children have been growing. Programs to protect the health of fetuses and children and the safety of the environment are being instituted, particularly in the USA and Europe. These regulations are mainly directed at foodstuffs and chemicals. The Experimental Radiobiology for Children's Health Research Group carries out studies to provide information on the risk of carcinogenesis due to radiation exposure during the fetal and childhood periods, for which there are at present insufficient data. Using animal models, we study the effects of radiation exposure on cancer induction and lifespan shortening. Final goals of this research group are to propose age-weighting factors and relative biological effectiveness (RBE) of neutrons and heavy ions for fetuses and children for radiation protection.

Progress of Research

1) Age dependency of life shortening by irradiation in B6C3F1 mice

Fifty female and male B6C3F1 mice per each group, which have been used in a wide variety of toxicological studies such as the National Toxicology Program (NTP) in USA, were exposed to gamma rays (^{137}Cs), carbon ions (13 keV/um) and neutrons (2 MeV) at various ages during fetal to mature adulthood periods. The ages examined were pre-implantation (3 days post-conception (dpc)), major organogenesis (13 dpc), late fetal (17 dpc), neonatal (1 week after birth), prepubertal (3 weeks), post-pubertal (7 weeks) and mature adult stages (15 weeks). The doses ranged between 0.2 and 4 Gy. These mice are now kept under observation. Preliminary observation indicated that female mice appeared more susceptible to radiation-induced lifespan shortening than male mice. Carbon ions were more potent in reducing lifespan than gamma rays when female newborn mice were exposed. Surprisingly, irradiation with gamma rays at late fetal stage had little influence on lifespan shortening, indicating fetuses are rather resistant to gamma-ray-induced lifetime risks compared to infant or adulthood exposure. However, when carbon ions were exposed, fetuses were as susceptible as infants. These results suggest a larger relative biological effectiveness (RBE) of carbon ions for fetus.

2) Age dependency of cancer risks in mammary gland, lung, bone marrow, liver, kidney, brain and intestine

Radiation risks are dependent upon tissues and age at exposure. Among tissues, breast tissue is most susceptible to radiation-induced cancer risk. In order to determine the age effect on mammary tumors, 821 female Sprague-Dawley rats, which have been widely used as a suitable model of human breast carcinogenesis, were irradiated with gamma rays and carbon ions (13keV/um) at doses of 0.2 and 1 Gy. We found an enhancement of tumor incidence after exposure at 3 weeks of age, which was in good agreement with the data of female A-bomb survivors. The tumor incidence after irradiation with carbon ions was almost identical or less than that after gamma-ray irradiation. No increase in mammary tumor incidence was observed in rats exposed prenatally. The lung is one of the important organs for radiological protection of workers and the public because of its high radiation-associated cancer risks. To elucidate the age dependence of its dose-effect relationship, 1, 5 and 15 week-old female Wistar rats (total 760 animals) were irradiated with X-rays at the thoracic region at doses of 0, 1, 3 and 5 Gy. It turned out that the older the rats were at exposure, the higher the incidence of lung tumors was. We also started new research on the age effect on tumor development of kidney, brain and

intestine using mutant and knockout animals such as the Eker rats and *Ptc*$^{+/-}$, *Apc*$^{Min/+}$, and *Mlh1*$^{-/-}$ mice. Kidney was found most susceptible at the perinatal period for radiation tumorigenesis.

3) Combined effect of radiation with chemical carcinogens on lung, uterine and thymic tumorigenesis

The age effect of combined exposures to radiation and a chemical carcinogen has been investigated on pulmonary, uterine and thymic carcinogenesis. Female Wistar rats were irradiated at infant (1 weeks of age), pubertal (5 weeks of age) and adult (15 weeks of age) stages followed by an intraperitoneal injection (1.0 g/kg body weight) of *N*-bis(2-hydroxypropyl)nitrosamine. The preliminary data indicated a synergism of radiation and chemical exposures when the former was in the pubertal stage. Uterine corpus cancer a typical fatal tumor in women, is increasing in many developed countries. For the age-dependent effects of irradiation on the uterine carcinogenesis, Donryu rats, were exposed to gamma-rays at doses of 0.2 and 2 Gy with or without *N*-ethyl-*N*'-nitro-*N*-nitrosoguanidine treatment during juvenile (2 weeks after birth) and adulthood (10 weeks after birth) stages. The rats exposed at prepuberty showed earlier onset of persistent estrus and, interestingly, an increase in uterine cancer development at 10 months of age. *Gpt*-delta mice were X-irradiated followed by *N*-ethyl-*N*-nitrosourea (ENU) treatment to see the mode of mutation induction after combined exposure. It was found that the mode was dose dependent. While combined exposures with a high dose of weekly irradiation (1.0 Gy per fraction for 4 weeks) enhanced lymphoma incidence in a synergistic manner, a small dose (0.2 Gy per fraction) suppressed lymphoma induction. The mutation induction was also suppressed by prior small dose exposure at 0.2 Gy ; this finding was in good agreement with lymphoma incidence. These results will provide the information on the relative risk and the age-weighting factor for radiation-induced carcinogenesis.

4) Detrimental effect of uranium on the childhood kidney

Health effects for children in depleted uranium-polluted areas and uranium mining areas are of recent concerns. Uranium and its compounds have the potential to cause nephrotoxicity. Using synchrotron radiation X-ray fluorescence analysis (SR-XRF) with a nano-probe, we demonstrated that uranium accumulated in the epithelium of the proximal tubules, a toxic target site of uranium, followed by an increase in apoptotic cells.

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2) T. Imaoka, M. Nishimura, S. Kakinuma, et al.: High relative biologic effectiveness of carbon ion radiation on induction of rat mammary carcinoma and its lack of H-*ras* and *Tp53* mutations, International Journal of Radiation Oncology Biology Physics, 69 (1), 194-203, 2007
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4) T. Takabatake, S. Kakinuma, T. Hirouchi, et al. : Analysis of changes in DNA copy number in radiation-induced thymic lymphomas of susceptible C57BL/6, resistant C3H and hybrid F1 mice, Radiation Research, 169 (4), 426-436, 2008
5) S. Homma-Takeda, Y. Nishimura, Y. Watanabe, M. Yukawa : Site-specific changes in zinc levels in the epididymis of rats exposed to ionizing radiation, Nuclear Instruments & Methods in Physics Research Section B, 260 (2), 236-239, 2007

5.3. Studies on Radiation Effect Mechanisms

Mitsuru Nenoi, Ph. D.
Director, Radiation Effect Mechanisms Research Group

Outline of Research Career

Dr. Nenoi received a Ph.D from Kyoto University in 1992 for his study on induced accumulation of polyubiquitin gene transcripts after UV-irradiation and TPA-treatment. His research interest is mechanisms of gene transcription after exposure to DNA damaging agents.

Objectives

Estimation of the low-dose radiation risk has been made using the high-dose data from atomic bomb survivors at Hiroshima and Nagasaki under the assumption that the risk is proportional to the radiation dose without a threshold. However, we do not necessarily have the scientific evidence to support this assumption. We do not have sufficient scientific data on the effects of low-dose radiation on developmental and differentiational anomalies either. Because it is now considered to be difficult to assess the risk of low-dose radiation from animal experiments or in epidemiological data, this research group conducts studies on the mechanism of radiation effects caused by low-dose radiation. The purpose of Radiation Effect Mechanisms Research Group is to derive findings useful in the risk assessment of low-dose radiation which can be used as a basis for the development of appropriate regulatory framework. The following study items are separately investigated by the four teams.

1) Radiation Carcinogenesis Research Team : Evaluation of indirect effects of low-dose radiation on carcinogenesis (carcinogenesis due to changes in the microenvironment caused by irradiation) and examination of the involvement of DNA repair mechanisms in low-dose radiation-induced carcinogenesis.
2) DNA Repair Gene Research Team : Clarification of low-dose radiation risk-modifying factors in nonhomologous end-joining DNA-repair and its molecular mechanism.
3) Developmental and Differentiational Anomaly Research Team : Verification of the validity of radiation regulations relating to developmental and differentiational anomalies by evaluating the effects of low-dose radiation on abnormalities in neural crest cell differentiation.
4) Radioadaptive Response Research Team : Determination of risk modifying factors specific to low-dose radiation by identifying genes associated with biological responses to low-dose radiation, including radioadaptive responses and signal transduction.

Progress of Research

1) Radiation Carcinogenesis Research Team

It has been thought that radiation-induced cancer is caused by radiation damage induced directly in the target cell. Because radiation causes mutations in the irradiated cells, cancer could occur if cancer-related genes are altered by irradiation. On the other hand, the existence of radiation-induced untargeted carcinogenesis, in which cancers originate from the radiation-induced change in a microenvironment in the irradiated body, has been known for 50 years, and the cause, the mechanism, and its contribution to the risk of the radiation-induced cancer have received attention in recent years. To confirm the existence of radiation-induced untargeted carcinogenesis and to evaluate its contribution to the risk of radiation-induced cancer, we first established an assay system for assessment of the indirect effect of radiation on carcinogenesis using thymus transplantation (Fig. 11). The thymectomized B10 thy1.2 mice were irradiated with 1.6 Gy γ-rays four times at one-week intervals and were transplanted with nonirradiated thymuses of new born B10 thy1.1 mice under the kidney capsule or subcutaneously. The mice were fed under a specific pathogen-free condition for one year and the generation of the T-cell lymphomas in the transplanted thymuses was observed. The origin of the tumors, which were derived from irradiated host cells or from nonirradiated thymic cells, could be determined using the expression of cell surface markers (thy1.1 or thy1.2) in the lymphoma cells. The incidence of thymic lymphomas in mice without thymectomy, which were irradiated four times with 1.6

Gy γ-rays, was 100%, which might include those induced by direct effect of radiation in target cells and those induced by radiation-induced microenvironmental change. The incidence of the transplanted thymus-derived T-cell lymphomas in mice irradiated and then transplanted subcutaneously was 33% (17/51), while that in mice irradiated and then transplanted under the kidney capsule was 50% (14/28). Thus both graft sites were effective in evaluating the indirect effect of radiation on carcinogenesis. There was no induction of T-cell lymphomas in mice transplanted with thymus, but not irradiated; this indicated that the generation of T-cell lymphomas from transplanted thymuses was due to the effect of radiation. These results confirmed the existence of radiation-induced untargeted carcinogenesis for the generation of T-cell lymphomas.

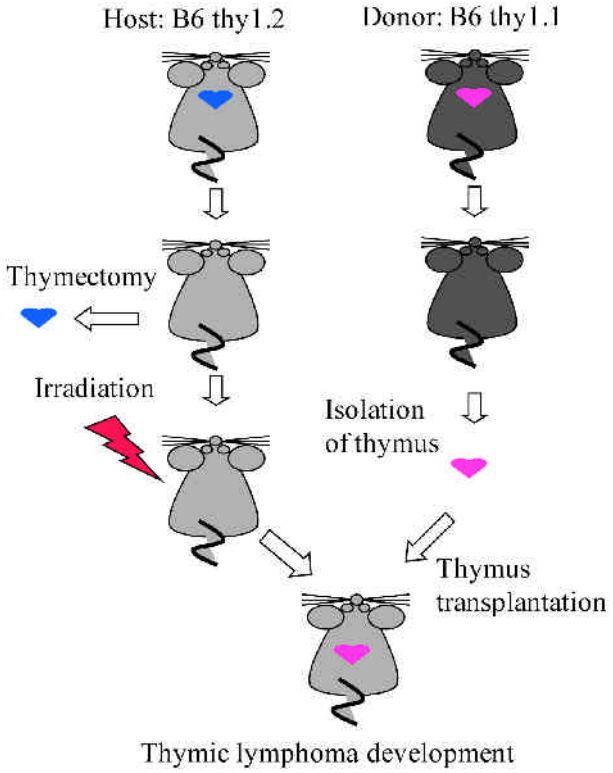

Fig. 11. Demonstration of untargeted lymphomagenesis using nonirradiated thymuses transplanted into irradiated mice

2) DNA Repair Gene Research Team

Our chief aim is to clarify the induction-mechanism of mutation by radiation. In particular, the identification of the modulatory factor (s) for a low-dose radiation-risk in non-homologous end-joining (NHEJ) and the elucidation of the molecular mechanism (s) involved with those factor (s) are the focus of our interest. DNA double strand breaks (DSBs) can arise from multiple sources including ionizing radiation (IR), and are the most serious DNA damage. NHEJ, which is a simple mechanism to piece together the broken DNA ends, can function in all phases of the cell cycle and it appears as the major repair pathway in mammalian cells. In the current study, we carried out the generation and characterization of NHEJ-related gene deficient human cell lines to define the biological roles of NHEJ-related genes on DNA damage induced by IR.

Three cell lines having *XRCC4*, *Artemis* and *MDC1* disrupted, respectively, were established by using a gene targeting technique in a human colon tumor cell line HCT116. Chromosomal aberrations induced by X-ray irradiation were significantly higher in all cell lines deficient in NHEJ-related gene than in parental HCT116. Radio-sensitivities assessed by the survival rate after X-ray exposure were apparently increased in these cell lines in comparison with the parental HCT116. These radiosensitive phenotypes might be due to insufficiency of DNA damage signaling/repair machinery in these deficient cell lines. Discrete foci of 53BP1, ATM (S1981), DNA-PKcs (S2056) and MDC1 formed in response to X-rays mostly co-localized to γ-H2AX foci, a marker of DNA DSBs, in the nucleus of the parental HCT116. The formations of 53BP1and ATM (S1981) foci, however, were not induced by X-ray exposure in *MDC1* deficient cells although positive immunoreactivities with specific antibodies were clearly detected throughout the nuclei of the deficient cells. Furthermore, foci of DNA-PKcs (S2056), relatively smaller than γ-H2AX foci, were formed after X-ray irradiation in *MDC1* deficient cells, but those foci did not co-localize to γ-H2AX foci. These results suggest that MDC1 may be associated with the recruitment of DNA damage signaling/repair components, such as ATM, DNA-PKcs and 53BP1, to sites of DNA DSBs induced by IR, and that MDC1 might be the master regulator determining the formation of a specific chromatin microenvironment required for genomic stability.

3) Developmental Anomalies Research Team

To elucidate the mechanism of the effects of low dose high LET radiations on the development of mice as well as neural crest-derived cells, melanocytes at cellular level, pregnant females of C57BL/10JHir mice at 9 days of gestation were whole-body irradiated with a single acute dose of argon ions. The effect was studied by scoring changes in the postnatal and prenatal development of mice as well as cutaneous coats 22 days after birth and in the melanocyte development in prenatal hair follicles. The percentage of births, the survival to day 22 and the body weight at day 22 were reduced in irradiated mice. By comparing the survival to day 22 for argon ions with that of γ-rays, argon ions were more than twice as effective as γ-rays. The frequency and the size of white spots (white haired skin devoid of melanoblasts and melanocytes) in the mid-

ventrum were increased in irradiated mice. Argon ions were more effective than γ-rays. In 18-day-old embryos, the frequency of abnormalities in the fore and hind legs, tails and eyes as well as of hemorrhage was increased as dose increased and the number of embryos and their body weight were decreased. In 18-day-old embryos, the development of hair follicles was also delayed as dose increased. These results suggest that argon ions seem to have a greater effect on postnatal and prenatal development of mice as well as on the melanocyte development than γ-rays.

4) Radioadaptive response research team

Radioadaptive response is a biodefensive response observed in a variety of mammalian cells and animals where exposure to low dose radiation induces resistance against the subsequent high dose radiation. The radioadaptive response implies that low dose radiation affects cells/individuals in a different manner from high dose radiation. Therefore elucidation of its mechanisms is important for risk estimation of low dose radiation. We investigated the molecular mechanisms for the radioadaptive response in terms of mutation at the HPRT gene locus using the human lymphoblastoid cells AHH-1. First we found that preexposure to the priming dose in the range from 0.02 Gy to 0.2 Gy significantly reduced mutation frequency at the HPRT gene locus after irradiation with 3 Gy of X rays, and that no significant adaptive response was observed with the priming dose of 0.005 Gy. Thus it was shown that the lower limit of the priming dose to induce radioadaptive response may be between 0.005 Gy and 0.02 Gy. Next, we examined the effect of 3-aminobenzamide (3AB), an inhibitor of poly (ADP-ribose) polymerase1, which has been reported to inhibit the radioadaptive response in terms of chromosome aberration. However significant radioadaptive responses in terms of mutation were observed even in the presence of 3AB, suggesting that molecular mechanisms of the radioadaptive response in terms of mutation may be different from that for radioadaptive responses in terms of chromosomal aberration. Alternatively we could not exclude the possibility that the differential effects of 3AB were due to cell type difference. Finally, by performing a comprehensive analysis of alterations in gene expression using HiCEP, we could identify 17 genes whose expressions were significantly altered 6h after irradiation with 0.02 Gy (Fig. 11). We also found 17 and 20 genes, the expressions of which were different with or without priming irradiations of 3 and 18 h, respectively, after challenge irradiation of 3Gy. By analyzing the gene function, it was found that expression of genes involved in intracellular signaling and redox-regulation is correlatively altered, and therefore can be considered the molecular basis of radioadaptive responses.

Major Publications

1. Ishii-Ohba, H., Kobayashi, S., Nishimura, M., Shimada, Y., Sado, T., Ogiu, T., Tsuji, H. : Existence of a threshold-like dose for gamma-ray induction of thymic lymphomas and no susceptibility to radiation-induced solid tumors in SCID mice, Fundamental and Molecular Mechanisms of Mutagenesis : A Section of Mutation Research, 619, 124-133, 2007
2. Koike, M., Mashino, M., Sugasawa, J. and Koike, A. : Dynamic change of histone H2AX phosphorylation independent of ATM and DNA-PK in mouse skin in situ. Biochem. Biophys. Res. Commun., 363, 1009-1012, 2007
3. Katsube, T., Tsuji, H. and Onoda, M. : Nitric Oxide attenuates hydrogen peroxide-induced barrier disruption and protein tyrosine phosphorylation in monolayers of intestinal epithelial cell. Biocimica et Biophysica Acta, 1773, 794-803, 2007
4. Hirobe, T., Abe, H., Wakamatsu, K., Ito, S., Kawa, Y., Soma, Y. and Mizoguchi, M. : Excess tyrosine rescues the reduced activity of proliferation and differentiation of cultured recessive yellow melanocytes derived from neonatal mouse epidermis. European Journal of Cell Biology, 86, 315-330, 2007
5. Kakimoto, A., Saito, T., Taki, K., Nakajima, T., Wang, B., Tanaka, K., Vares, G., Wu, J., Sakai, K., Nenoi, M. : Molecular mechanisms of radioadaptive responses in human lymphoblastoid cells. RADIOISOTOPES, 57, 99-110, 2008

Table 1 Number of transcripts whose expression levels were significantly altered in cells treated with priming dose (0.02 Gy) 6h before challenge irradiation.[a)]

Time of RNA sampling	Number of transcripts			
	Identified[b)]		Unidentified[c)]	Total
	Unique[d)]	Multiple[e)]		
immediately before challenge irradiation	17	44	3	64
3h after challenge irradiation	17	58	5	80
18h after challenge irradiation	20	72	8	100

a) Gene expression was considered to be significantly altered when either one of analyses using equally divided RNA samples from 0.02 Gy-irradiatd cells showed fold-change larger than 2 or less than 0.5.
b) Transcripts, for which the gene was identified based on the size of the Msp1-Mse1 fragments.
c) Transcripts, for which no gene was identified based on the size of the Msp I-Mse I fragments.
d) Transcripts, for which the gene was uniquely identified.
e) Transcripts, for which the gene was not uniquely identified.

5.4. Studies on Environmental Radiation Effects

Satoshi Yoshida, Ph. D.
Director, Environmental Radiation Effects Research Group

Outline of Research Career :

Education : 1983, Yokohama National University (BE in safety engineering) ; 1985, Tokyo Institute of Technology (ME in environmental chemistry) ; 1989, Tokyo Institute of Technology (Ph. D. in environmental chemistry)

Professional Activities: 1989-present, National Institute of Radiological Sciences

Research Interests: Radioecology, environmental chemistry, and ecotoxicology

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Objectives

The recent rapid changes in energy production systems and life styles of people worldwide have made environmental radiation research even more important. In order to satisfy the needs for radiation safety and regulations, Environmental Radiation Effects Research Group investigates three subjects related to environmental radiation and radioactivity : 1) effects of radiation on organisms and ecosystems; 2) exposure of public to natural radiation ; and 3) marine dynamics of important radionuclides. The group consists of five research teams : Terrestrial Radiation Ecotoxicology Research Team, Aquatic Radiation Ecotoxicology Research Team, Natural Radiation Exposure Research Team, Cosmic Radiation Exposure Research Team, and Marine Radioecology Research Team. The following describes the progress of each of these teams during FY 2007.

Progress of Research

1) Effects on organisms and ecosystems

While the importance of radiological protection of the environment based on scientific principles is increasingly recognized internationally as environmental issues garner more attention, the relevant scientific data are extremely limited. This group conducts studies to evaluate the effects of radiation on representative terrestrial and aquatic organisms as well as studies to estimate radiation dose on those environmental organisms. In addition, the group develops methods to evaluate the ecological effects of radiation using experimental model ecosystems containing various species.

a) Terrestrial Radiation Ecotoxicology Research Team

To understand the impact of radiation on terrestrial ecosystems, plants (particularly cedar tree), fungi, earthworms and springtails were selected and the dose-effect relationships for radiation have been studied. Recently, gene expression as a biomarker has been receiving increased attention in the ecotoxicological research field as it may produce fast, sensitive and diagnostic assays. Therefore, the study to detect radiation responsive genes was started as a new research direction. A novel technology, high-coverage expression profiling (HiCEP), developed by the researchers in NIRS, was applied in the springtail *Folsomia candida* (Collembola) in which the dose-effect relationships for radiation on survival, growth and reproduction were already estimated. A HiCEP analysis showed that several transcript-derived fragments (TDFs) were up-regulated by irradiation in *F. candida*, and sequencing the TDFs revealed that a few of them were similar to genes relating to DNA repair and response to oxidative stress. For the other TDFs, no similarity was found in the gene database, probably because of the limited length of TDFs or limited genome information in springtails. These findings suggest that HiCEP is effective at discovering both known and unknown TDFs, even in non-genomic model organisms such as *F. candida*. HiCEP was also applied to an established cell line derived from a cedar tree.

b) Aquatic Radiation Ecotoxicology Research Team

The studies on the radiation effects of aquatic ecosystems at various end points were carried out by using some selected organisms and ecosystems including experimental model ecosystems.

In order to evaluate ecological effects at the community-level, the multi-species microcosm consisting of eight identified microorganisms and bacteria was acutely irradiated with gamma rays at

100, 500, 1000 and 5000 Gy, and effects on populations were observed. Effects observed in the microcosm were not only direct effects but also indirect effects due to interspecies interactions. The results were analyzed using the ecological effect index (EEI), in which degrees of differences in the population densities between exposed and control microcosms were represented by the Euclidean distance function. A 50 % effect dose for the microcosm (ED_{M50}), at which the EEI became 50 %, was evaluated to be 2000 Gy for gamma rays when the microcosm was exposed in the developing stage. The ED_{M50}s evaluated for copper and 2,4,5-T (herbicide) were 0.57 mg/l and 49 mg/l, respectively.

Evaluation of radiation effects on soil bacteria by using conventional methods based on cultivation of isolated bacteria is difficult, since more than 90% of the bacteria existing in soil cannot be cultured on laboratory media. To overcome the drawbacks of these culture-dependent methods, molecular techniques have been widely used in the last decade. In our study, Denaturant Gradient Gel Electrophoresis (DGGE) based on the 16S rRNA gene sequence was applied to estimate the effect of ionizing radiation on soil bacterial community. Our results showed that chronic gamma irradiation at a dose rate of 1.2 Gy/d to a paddy soil system (total dose 6 Gy) changed the structure of bacterial community. Although it is thought that bacteria are less sensitive to radiation exposure, metabolic activities of soil bacteria would be sensitive. Enhancing knowledge of those radiation effects will aid in the development of environmental radiation protection at the ecosystem level.

2) Exposure to natural radiation

Since natural radioactive substances and cosmic radiation at high altitude contribute greatly to the radiation dose received by the general public, it is necessary to quantify the actual level of exposure and to document its features. The group therefore investigates the concentration and exposure doses of radon (^{222}Rn), thoron (^{220}Rn), and related radionuclides, mainly in areas with high natural radiation, and analyzes the results together with epidemiological data. The group also aims to collect scientific information on dose and effects of cosmic radiation in aircraft and to provide them in an intelligible way for the general public such as on the Internet.

a) Natural Radiation Exposure Research Team

A preliminary survey on indoor radon/thoron and external gamma ray dose rate was conducted for houses in Gejiu city/Toudaoshui village in Yunnan Province, China. Although several studies have been conducted to investigate the relationship between lung cancer risk and radon exposure for tin miners in this area, previous studies did not take note of the presence of thoron. Thus, discriminative measurements of radon/thoron and their progeny measurements were conducted in the present study. The measurements can be divided into short-term and long-term measurements. For the short-term measurement, a Japan-China joint research team investigated several houses using some active devices such as a pulse-ionization chamber (AlphaGUARD). For the long-term measurement, radon/thoron discriminative monitors (RADOPOT) were placed for about 50 houses. The monitors were retrieved after a few months' exposure and radon/thoron concentrations were estimated. Deposition rate monitors for measuring thoron progeny concentration were also placed in 30 houses. Similarly, these monitors were retrieved after a few months' exposure and EETC (Equilibrium Equivalent Thoron Concentration) was estimated.

The measurement results are summarized as follows : (1) radon concentration for 49 houses ranged from 32 to 498 Bq/m^3 with an arithmetic mean of 136 Bq/m^3; (2) thoron concentration for 49 houses ranged from 39 to 7,908 Bq/m^3 with an arithmetic mean of 3,297 Bq/m^3; (3) EETC for 29 houses ranged from 2.0 to 23.9 Bq/m^3 with an arithmetic mean of 10.2 Bq/m^3; (4) Equilibrium Equivalent Radon Concentration (EERC) for 6 houses ranged from 8 to 44 Bq/m^3 with an arithmetic mean of 25 Bq/m^3; and (5) gamma ray dose rate ranged from 0.09 to 0.17 μSv/h with an arithmetic mean of 0.11μSv/h. Very high thoron concentrations were found in many houses in this area. Further dosimetric and epidemiological studies are needed to investigate the possible effects of radon and thoron.

b) Cosmic Radiation Exposure Research Team

More than 16 million Japanese people go abroad every year using aircraft and about 20 thousand people are members of aircraft crews in Japanese airline companies. At high altitude, they are exposed to enhanced cosmic radiation, and additional radiation dose can exceed 1 mSv per year. However, the situation and the health effects of cosmic radiation exposure are still uncertain. The team thus makes efforts to collect scientific information on dose and effects of cosmic radiation and also to provide them in an easy-to-understand way by the general public. Major tasks are (1) calculation of route doses (effective doses received in aircraft) using the most up-to-date method, (2) development of new detectors to verify calculation results, and (3) improvement of dosimetry system for radiological protection of

aircraft crew. Some results obtained by the team are open to the public from the NIRS web site "Japanese Internet System for Calculation of Aviation Route Doses (JISCARD) ". In 2007, an original simulation model which can determine precisely cosmic radiation intensities at aviation altitudes was developed in collaboration with the Japan Atomic Energy Agency. Using this new model, the global map of real-time dose rates at aviation altitudes were provided on the web for the general public. We also developed a neutron irradiation field of ^{241}Am-Be for calibration of the detector assembly used for validation of the model simulation. We are cooperating with airline companies in Japan, regarding to education and radiation exposure management of aircraft crew members.

3) Marine dynamics of important radionuclides

Because many Japanese nuclear facilities are located in coastal areas facing the Pacific Ocean and the Japan Sea, it is very important to predict the environmental behavior, and thus the fate of radionuclides in marine ecosystems. The group focuses on the development of highly sensitive analytical methods for important radionuclides (e. g., plutonium, americium, iodine etc.) for which data are scarce, and provides data on their activities and isotopic ratios to understand their environmental behavior in marine ecosystems.

a) Marine Radioecology Research Team

A rapid and simple isotope dilution sector-field ICP-MS analytical method was developed in order to obtain precise ^{241}Am concentration in marine sediment samples. The separation and purification of ^{241}Am was achieved using a selective CaF_2 co-precipitation followed by a TRU extraction chromatography. For the first time, we achieved an extremely low detection limit (0.32 fg/g or 0.041 mBq/g) which is even better than that of alpha spectrometry. The major advantages of our method can be summarized as: rapid sample preparation (1-2 days), less waste generation, high precision, and excellent detection limit.

Surface seawater samples were collected from a site in the vicinity of the nuclear fuel reprocessing facility at Rokkasho, Japan and sites along the Japan Sea coast. $^{239+240}$Pu activities and ^{240}Pu/^{239}Pu atom ratios were determined by α-spectrometry and isotope-dilution sector-field ICP-MS. The atom ratios of ^{240}Pu/^{239}Pu in coastal surface seawater, ranging from 0.221 ± 0.019 to 0.235 ± 0.023, were significantly higher than the mean global fallout ratio of 0.18. The contribution of the Pacific Proving Grounds (PPG) close-in fallout Pu was estimated to be 33 % using a two end-member model. It was proposed that the oceanic currents accounted for delivery of close-in Pu from the PPG to the studied areas. ^{239}Pu and ^{240}Pu derived from the two sources of global fallout and close-in fallout were homogenized in the surface water of the Pacific coast and Japan Sea coast. Data on ^{240}Pu/^{239}Pu atom ratios in seawater samples collected in the vicinity of the Rokkasho nuclear fuel reprocessing plant will provide useful keys for understanding the process controlling plutonium transport and for distinguishing potential sources of Pu.

Major Publications

1) T. Nakamori, S. Yoshida, Y. Kubota, et al.: Effects of acute gamma irradiation on *Folsomia candida* (Collembola) in a standard test, *Ecotoxicology and Environmental Safety*, 71, 590-596, 2008
2) N. Ishii, S. Takeda, K. Tagami, S. Fuma, H. Takeda : Application of droplet-PIXE system to study radiation effects on ecosystem functioning, *International Journal of PIXE*, 17, 161-167, 2007.
3) T. Ishikawa, S. Tokonami, et al : Calculation of dose conversion factors for thoron decay products, *Journal of Radiological Protection*, 27, 447-456, 2007.
4) K. Yajima, H. Yasuda, T. Suzuki : Construction of a gamma-ray and neutron irradiation field, *Radioisotopes*, 57, 167-174, 2008 (in Japanese).
5) M. Yamada, J. Zheng: Determination of ^{240}Pu/^{239}Pu atom ratio in coastal surface seawaters from the western North Pacific Ocean and Japan Sea, *Applied Radiation and Isotopes*, 66, 103-107, 2008.

5.5 Office of Biospheric Assessment for Waste Disposal

Shigeo Uchida, Ph. D.
Head, Biospheric Assessment for Waste Disposal

Outline of Research Career

Dr. S. Uchida received his doctoral degree from Kyoto University. He has about thirty years' experience in the fields of radioecology and environmental radiochemistry ; his special interest is the behaviors of long-lived radionuclides in the environment, e. g., ^{63}Ni, ^{79}Se, ^{90}Sr, ^{99}Tc, ^{129}I, ^{137}Cs, Th, U, etc. He has improved models and parameters for radionuclides in soil-to-crop systems. He has been proceeding with a project to collect and estimate environmental transfer parameters of radionuclides in relation to radioactive waste management.

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Objectives

The biospheric assessment of radiation dose to human beings related to the releases of long-lived radionuclides from underground nuclear waste disposal sites is very important for the peaceful use of atomic energy. For the assessment, radioecological transfer models and transfer parameters are needed. Environmental conditions, such as climate, vegetation and soil, affect these parameters. Additionally, agricultural products and food customs in Japan differ from those in Europe and North America. Therefore, we should collect our own practical data in Japan using data from European and North American countries as references.

In this office, environmental transfer parameters, such as soil-to-crop transfer factors (TFs) and soil-soil solution distribution coefficients (K_d s), have been collected from agricultural fields throughout Japan for 5 years. TF is defined as the ratio of activity concentration in plant to activity concentration in soil, while K_d describes the behavior of radionuclides in the soil in terms of the ratio of concentrations in the soil solid and soil-solution phases. Analyses of stable isotopes and some natural radioisotopes in crops and their associated soils have been carried out in order to obtain TFs under equilibrium conditions, while radiotracer experiments have been applied for K_ds in various soils. Since rivers are one of the most important paths of radionuclide transfer from waste disposal sites to agricultural fields, chemical components of major Japanese rivers have also been determined and we published the data book entitled *"Elemental Concentrations of Japanese Rivers* (NIRS-M-200) ". In addition, transfer models for predicting radionuclides' behavior in atmosphere-paddy soil-rice plant systems have been developed.

Progress of Research

1) Soil-Soil Solution Distribution Coefficients For Se, Sr, Sn, Sb, and Cs in Japanese Agricultural Soils

In agriculture, K_d is particularly important for assessing potential crop uptake of various elements. The K_d value depends on which radionuclide is being modeled, the soil group, and soil properties. In order to obtain practical K_d values, it is necessary to obtain K_ds for each important radionuclide in many types of soils. In addition, this parameter should be used to determine which soil properties are important factors that determine the variation in K_d for each radionuclide. Many previous studies have used K_d values, but a few studies have collected sufficient K_d data to permit a statistical analysis. In this study, therefore, K_ds for five radionuclides (Se-75, Sr-85, Sn-113, Sb-124, and Cs-137) were determined by batch sorption tests in 142 Japanese agricultural soil samples (63 paddy soil and 79 upland soil samples).

The results showed that Se- and Sb-K_d data did not have normal or log-normal distributions, but Sr-, Sn-, and Cs-K_d data had log-normal distributions (Fig. 12). Further, Se-, Sr-, and Cs-Kd values differed between paddy and upland soil samples by t-test ($p < 0.05$). Spearman's rank correlation test was carried out to investigate correlations between K_d values for each radionuclide and soil properties. Combinations of K_d value and soil property having the highest correlation coefficient (R_S) for each radionuclide were as follows : Se-K_d - concentration of water soluble P (R_S = -0.51) ; Sr-K_d - concentration of water soluble Ca (R_S = -0.57) ; Sn-K_d - concentration of water soluble Sr (R_S = 0.57) ; and Sb-Kd - concentration of water soluble P (R_S = -0.67). Although there were no soil properties which had a good correlation with Cs-K_d values for all soil samples, the best correlated soil property with Cs-K_d values was concentration of water soluble ammonium

ion (Rs = -0.48) for upland soil samples.

2) Soil-to-crop Transfer Factors of Radium in Japanese Agricultural Fields

Radium-226 (^{226}Ra), an alpha emitter with a half-life of about 1600 y, is a natural decay product of ^{238}U. Radium-226 is of special interest because it is an important radionuclide for the assessment of radioactive waste disposal. This radionuclide can reach humans through several transfer paths in the environment. Once Ra is taken into the human body by ingestion of food and water or inhalation, it can distribute into bone where it has a long biological half-life ; exposure to Ra can cause cancers and other body disorders. Therefore its long-term management is required and understanding of Ra behavior in the environment is important, especially its soil-to-crop transfer that directly affects the internal radiation dose assessment for the ingestion pathway. Although ^{226}Ra exists in the environment, due to its low concentration in crops, TFs that have been obtained from agricultural fields are limited. In many cases, therefore, TFs used in such models were from the technical report series 364 (TRS-364) compiled by IAEA. These data were obtained in temperate zones mainly from Europe and North America, and thus, the numbers of TFs for rice and crops native to Japan were limited. In this study, we determined the concentrations of ^{226}Ra in upland field crops (leafy vegetables, onion, potato, and so on) and associated soils collected from 45 locations throughout Japan in order to obtain TFs. We also measured alkaline earth metal concentrations to compare their behavior with Ra, which is the last member of this group and whose lighter members, Mg and Ca, are plant nutrients.

The results are summarized in Table 1. Concentrations of ^{226}Ra in the soils collected in southwestern Japan were higher than those in northeastern Japan; however, no correlations between ^{226}Ra concentrations in crops and soils were observed. The TFs ranged from $<1\times10^{-3}$ to 5.8×10^{-2} with a geometric mean of 6.4×10^{-3}. These data were within the 95% confidential range of TF-Ra for several crops as reported in the IAEA TRS-364. Among the alkaline earth metals, TF-Ba was similar to TF-Ra.

3) Estimation of Anthropogenic Uranium Amount in 112 Japanese Agricultural Soil Samples due to Application of Phosphatic Fertilizers

Uranium (U) and thorium (Th) behavior in geological environments are relatively close to each other compared to their behaviors and those of other elements. Thus high relationships between their concentrations are usually observed in rocks, non-agricultural field soil samples and river sediments, etc. Indeed, in Japan the concentration ratios of U/Th in these environmental samples, were almost the same, being about 0.20-0.28. However, applications of phosphatic fertilizers to agricultural fields might increase their U concentration since the fertilizers are known to be high in U content (fertilizer U contents are 10-300 times higher than U contents in uncontaminated soils) but low in Th content. Thus the U/Th ratios in phosphatic fertilizers are significantly higher than the natural U/Th ratio.

In order to estimate the excess amount of U (U_{ess}) in agricultural fields, it is necessary to obtain native U concentrations in those fields. Natural U/Th ratio in non-agricultural fields would be useful to estimate content of Uess in agricultural fields. Concentrations of U and Th in soil are closely related to the original materials of the soil, but U is more mobile than Th is so that the natural U/Th ratio in non-agricultural fields is slightly lower than the parent rock. From the average composition of the Japan upper crust, the U/Th ratio is 0.28, but in non-agricultural fields, 0.22-0.25 ratios were observed.

In this study, we estimated U_{ess} in Japanese agricultural fields due to phosphatic fertilizer application by using inductively coupled plasma mass spectrometry (ICP-MS) to measure concentrations of total U and Th in 112 agricultural soil samples (50 paddy field and 62 upland field soil samples). The samples were collected throughout Japan.

The average concentrations of total Th and U in the paddy field soil samples were 5.7 mg kg^{-1} and 2.8 mg kg^{-1}, respectively, while those in the upland field soil samples were 2.6 mg kg^{-1} and 5.5 mg kg^{-1}, respectively. These Th and U concentrations showed no differences between paddy field and upland field soil samples. Concentration ratios of U/Th in paddy field and upland field soils were 0.53 and 0.52 on average, respectively, which were much higher than those in Japanese non-agricultural fields (0.23). The results implied that phosphatic fertilizers, which have high U concentrations, increased the total U concentration in the agricultural fields. Thus, using the natural U/Th ratio in non-agricultural areas, we estimated the excess amount of U. About 52% of total U in paddy field soils (ca. 1.5 mg kg^{-1} of U on average) and 50% of total U in upland field soils (ca. 1.3 mg kg^{-1} of U on average) were calculated as excess amounts of U. Thus using of phosphatic fertilizers in agricultural fields makes only a small contribution as external radiation to the general population.

Major publications

1) S. Uchida, K. Tagami, and I. Hirai : Soil-to-Plant Transfer Factors of Stable Elements and Naturally Occurring Radionuclides : (1) Upland Field Crops Collected in Japan, J. Nucl. Sci. Technol.,

44, 628-640, 2007.
2) S. Uchida, K. Tagami, and I. Hirai : Soil-to-Plant Transfer Factors of Stable Elements and Naturally Occurring Radionuclides : (2) Rice Collected in Japan, J. Nucl. Sci. Technol., 44, 779-790, 2007.
3) S. Uchida, K. Tagami: Soil-to-crop transfer factors of radium in Japanese agricultural fields, Journal of Nuclear and Radiochemical Sciences, 8, 137-142, 2007
4) N. Ishikawa, K. Tagami, S. Uchida : Sorption kinetics of selenium on humic acid, J. Radioanal. Nucl. Chem., 274, 555-561, 2007.
5) Y. NAKAMARU, N. Ishikawa, K. Tagami, and S. Uchida: Role of soil organic matter in the mobility of radiocesium in agricultural soils common in Japan, Colloids and Surfaces A : Physicochemical and Engineering Aspect, 306, 111-117, 2007.

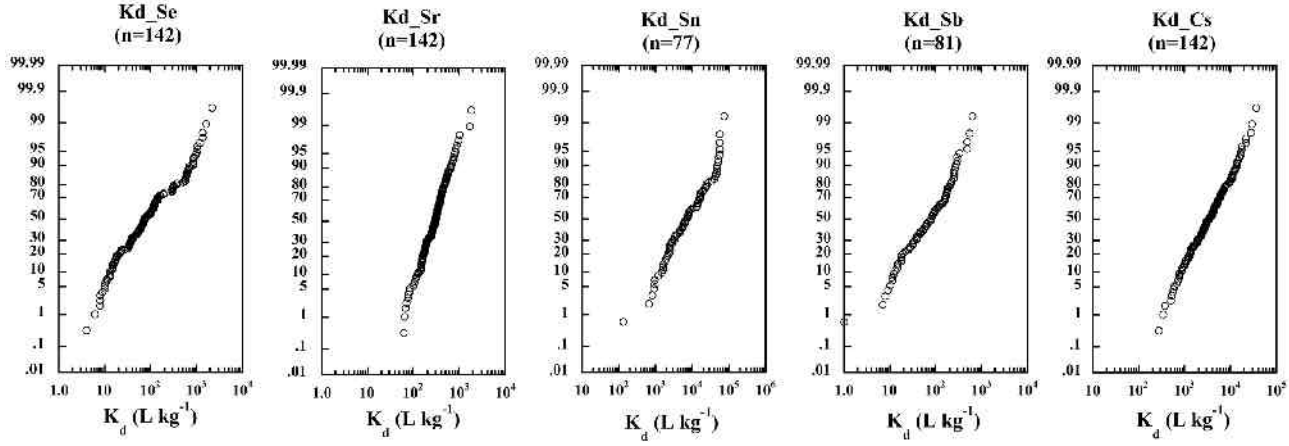

Fig. 12. Probability distributions of Kd values of the five radionuclides.

Table 2 : Concentrations of ^{226}Ra in soil and crop samples on dry weight basis and transfer factors.

Crop name	N*1	Concentration range (Bq/kg-dry)		TF range
		Soil	Crop	
Cabbage	5	20.5 - 39.0	0.11 - 0.59	(0.5 - 2.3) x 10^{-2}
Chinese cabbage	2	13.9 - 36.5	0.47 - 0.59	(1.3 - 4.3) x 10^{-2}
Lettuce	2	30.9 - 41.7	<D. L. - 0.32	<D. L. - 0.8 x 10^{-2}
Spinach	1	28.8	0.23	0.8 x 10^{-2}
Carrot (leaves)	1	42.8	1.15	2.7 x 10^{-2}
Japanese radish (leaves)	1	60.3	0.46	0.8 x 10^{-2}
Leak (green part)	8	16.5 - 29.9	<D. L. - 1.72	<D. L. - 5.8 x 10^{-2}
Onion	3	26.1 - 43.9	<D. L. - 0.15	<D. L. - 0.3 x 10^{-2}
Japanese radish	3	33.7 - 60.3	0.22 - 0.52	(0.4 - 1.5) x 10^{-2}
Carrot	1	42.8	1.43	3.3 x 10^{-2}
Potato	5	22.7 - 48.9	0.04 - 0.12	(0.1 - 0.3) x 10^{-2}
Sweet potato	2	16.0 - 28.5	0.04 - 0.05	(0.2 - 0.3) x 10^{-2}
Taro	2	39.3 - 45.5	<D. L. - 0.11	<D. L. - 0.2 x 10^{-2}
Cucumber	1	29.1	0.21	0.7 x 10^{-2}
Sweet pepper	2	30.8 - 33.3	<D. L. - 0.11	<D. L. - 0.3 x 10^{-2}
Tomato	2	41.9 - 43.5	<D. L.	<D. L.
Egg plant	2	19.6 - 41.8	<D. L. - 0.09	<D. L. - 0.2 x 10^{-2}
Soybean	1	30.0	0.10	0.3 x 10^{-2}
Peanut	1	17.5	0.12	0.7 x 10^{-2}
Wheat	3	24.9 - 41.5	0.06 - 0.17	(0.1 - 0.5) x 10^{-2}
Barley	2	31.9 - 34.3	<D. L. - 0.05	<D. L. - 0.2 x 10^{-2}

* **1** : Number of observations

6. Research Center for Radiation Emergency Medicine

Makoto Akashi, M.D., Ph. D.
Director, Research Center for Radiation Emergency Medicine

Outline of Research Career :

Dr. Akashi started his medical career at Jichi Medical School (Tochigi Prefecture) as a junior resident of internal medicine in 1981. He next worked as a senior resident in the Division of Hematology of Jichi Medical School and in 1987 moved to the Division of Hematology/Oncology at UCLA School of Medicine in 1987. He received a Ph. D. from Jichi Medical School in 1988. He has been a staff member of NIRS since 1990. His major studies are: 1) Establishment of radiation emergency medical preparedness ; 2) research on radiation injuries, including molecular and cellular mechanisms ; and 3) development of methods for mitigation of radiation injuries. He has treated patients of the criticality accident in Tokai-mura.

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Objectives

This Research Center had the unique experience of receiving three victims heavily exposed at the JCO criticality accident of Tokai-mura in September 1999, because the Center has been assigned as the national center for radiation emergency medical preparedness by the Nuclear Disaster Prevention Plan of the Japanese government since 1980. The Center is responsible for, and has established a solid system for dealing with a radiation emergency from the point of medicine.

Our required aims to satisfy the plan are as follows :

- to receive victims exposed to radiation who require specialized diagnosis and treatment;
- to dispatch a radiation emergency medical team to local emergency medical headquarters;
- to facilitate exchange of information, research activities, and human resources, by constructing networks in cooperation with other organizations who could deal with a radiation emergency;
- to maintain and reinforce an efficient radiation emergency medicine system under usual conditions;
- to promote technical development and research on radiation emergency medicine; and
- to develop skilled manpower for a radiation emergency.

Other objectives of the Center are related to research on radiation emergency medicine. Details are given elsewhere; only subjects are presented here.

1. Research for diagnosis and treatment of exposure to high-dose radiation
   1-1 Studying mechanisms of radiation injuries leading to developing new agents for treatment with focus on the skin and gastrointestinal tract
   1-2 Studying indicators of radiation exposure dose from biological specimens
2. Research on dose assessment for victims in radiation accidents

Overview

After the nuclear accident at Three Mile Island in 1979, the Central Disaster Prevention Council (CDPC) in the Prime Minister's office reinforced emergency preparedness for dealing with a nuclear power station emergency and issued a report "Urgent Disaster Countermeasures to be taken for Nuclear Facilities by Governmental Agencies" in July, 1979. In June 1980, the Nuclear Safety Commission (NSC) came up with a guideline entitled "Off-site Emergency Planning and Preparedness for Nuclear Power Plants." This guideline nominated NIRS as a tertiary radiation emergency hospital that serves as the final stage hospital for receiving victims heavily exposed to radiation and/or contaminated with radionuclides due to nuclear or radiological accidents. From January 2004 the Research Center has served as a liaison institution of WHO/REMPAN (Radiation Emergency Medical Preparedness and Assistance Network).

The Research Center carries out the following activities to maintain and enhance or strengthen the emergency preparedness system required to fulfill its role as the tertiary radiation emergency hospital.

1) Network System

The primary goal is strengthening its institutional system to prepare for radiation emergencies by establishing three nation-wide network councils, for medicine, chromosome analysis as bio-dosimetry, and physical dosimetry.

a) NIRS Radiation Emergency Medicine Network Council

This is a group of experts and medical organizations from which NIRS asks for help to treat

the victims at the time of a nuclear disaster or a radiological accident. The cooperation involves sending an expert in the specific field in an emergency, arrangement of acceptance of patients at medical facilities affiliated with the expert's organization, and provision of advice. Such collaboration is expected to reinforce the functions of NIRS. NIRS will call the Radiation Emergency Medicine Network Council to solicit cooperation when it is requested by authorities (or when NIRS thinks the necessity arises) to respond to radiation emergencies. This council worked effectively at the time of the JCO criticality accident in 1999.

b) Chromosome Network Council

This council forms a network among a limited number of experts having dose evaluation capability based on chromosome analysis. Through this network, NIRS can strengthen the capability of the dose estimation by chromosome analysis, and also establish the technical standards of dose estimation method by chromosomes.

c) Physical Dosimetry Network Council

This council is a network of experts in physical dose evaluation. The network is expected to respond to emergencies through collaboration among experts for prompt and precise dose estimation. It is also responsible for accumulating dose evaluation technology and for fostering followers.

d) Local Medicine Network Council

In Japan, medical systems for radiation emergencies are currently being constructed in accordance with disaster prevention plans of local governments that have nuclear facilities in their territories. Within the framework of each local nuclear disaster prevention plan, establishment of a specific collaboration system with NIRS is mandatory and the ststem must specify the steps to be performed in the smooth transfer of patients from a site to a hospital, including radiation protection management at the hospital.

2) Training

The primary goal for training is the development of radiation emergency medicine skills for medical professionals and disaster responding personnel; these include doctors and nurses involved in nuclear disaster medical care, emergency crews, and nuclear establishment employees. For that purpose the following training courses are regularly held in addition to our participation in nuclear disaster prevention training, seminars on medical response and other activities conducted by local governments to provide the relevant information and skills to deal with a radiation emergency.

a) Radiation emergency medicine course (hospital course)

This 3-day course is designed for physicians, nurses, radiologic technologists who may receive victims exposed to radiation and/or contaminated with radionuclides. The course is held three times a year with 20 participants in each course. More than 320 participants have been trained so far. Many of them are working actively in primary or secondary levels of radiation emergency hospitals and playing an important role in local radiation emergency exercises.

b) Emergency rescue training course (pre-hospital course)

This 3-day course is primarily designed for first responders such as fire or police personnel, paramedics, and emergency planners at nuclear facilities. The course is held four times a year with 30 participants in each course.

c) Training course for the WBC

This 3-day course is intended for personnel working in health physics, medical physics, radiation safety and others who have radiation dose assessment responsibilities. The course presents an advanced level of information on radiological/nuclear event reconstruction and dose assessments/ estimations, focusing on internal contamination. Topics related specifically to radiation emergency medicine include internal and external contamination. Other topics covered include internal and external dosimetry and bioassay techniques.

This course is held once a year with 18 participants.

3) Emergency Exercises

National and local governments annually hold drills for nuclear emergency. NIRS sends staff members to these drills to give advice from the medical or radiation protection point. On 24 October 2007, the Japanese government conducted a nuclear drill at Japan Nuclear Fuel Ltd. 's reprocessing plant for spent nuclear fuel (Rokkasho-mura, Aomori Prefecture) to enforce readiness for a criticality accident. About 1,800 people from some 70 organizations participated in the drill, including medical doctors and experts on radiation protection from NIRS. The daylong drill was conducted assuming nuclear chain reactions were triggered from mishandling fuel and equipment that caused radioactive leaks. A mock victim was transferred from the plant to NIRS using a plane of the Japan Self Defense Force and a helicopter of Fire Department, the Chiba City government. Following the drill, NIRS conducted an additional exercise to simulate emergency handling, especially dose assessment.

4) Follow-up Studies

The Research Center for Radiation Emergency

Medicine conducts research work in a wide range of areas: medical care, radiation measurement and investigation, health physics, cytogenetics, and psychology. In addition, we study dose evaluation which facilitates decision-making in treatment for high-dose exposure or reduction of high-dose exposure effects, identification of radionuclides, and rapid evaluation of population exposure.

The Center also carries out medical follow-up for the victims who were exposed to radiation in the thermonuclear weapon test on the Bikini Atoll, patients with thorotrastosis, and a surviving JCO accident victim.

a) Follow-up examination of the victims of the Bikini nuclear test

On March 1, 1954, the 23 crew members (18 to 39 years old at the time) of the Japanese fishing vessel Daigo Fukuryu Maru, or "Lucky Dragon", out of Yaizu City, Shizuoka Prefecture watched a bright light in the South Pacific as the sun began rising. Seven or eight minutes later there was a terrific sound. They did not know what it was at the time. The blast, equivalent to about 12 million tons of TNT, was 750 to 1,000 times more powerful than the atomic bomb dropped on Hiroshima. All 23 were hospitalized after returning to Japan. One of them died of liver failure seven months later. Several hundred inhabitants of the Marshall Islands in the Pacific, as well as nearly 30 U. S. personnel involved in the tests, were also injured from the nuclear fallout.

This medical follow-up examines the health states of these patients over a long period of time in order to study late radiation effects. The follow-up examinations that have been conducted for 50 years provide important information. The type of exposure was external and also internal, although internal doses were thought to be relatively small. The estimated whole body doses were 1.7 to 6.0 Gy. Among the Lucky Dragon victims, 12 have now died. Causes of death are as follows: liver cancer, 6; liver cirrhosis, 2; liver fibrosis, 1; colon cancer, 1; heart failure, 1; and traffic accident, 1.

This year, physical check-ups of survivors were conducted at NIRS and Yaizu City Hospital. Six persons were checked at these facilities. Malignancies were suspected in two of these people. Many of them have evidence of infections by hepatitis viruses since all victims received transfusions in 1954.

NIRS held a symposium in Chiba on "The Fifth Lucky Dragon at the Bikini Atoll" in collaboration with the Japanese Radiation Research Society and discussed aspects of the accident.

b) Follow-up examination of patients with thorotrastosis

Thorotrast is an alpha particle-emitting thorium dioxide colloid, which was used clinically in the 1930s and 1940s as a radiographic contrast medium. It was injected intravascularly for the visualisation of vascular structures. Long-term retention of thorotrast in the reticuloendothelial system, in the liver, spleen and bone marrow produces lifetime alpha particle irradiation of these organs. Considerable epidemiological follow-up has been performed on patients given the contrast, mainly German, Danish and Japanese patients and it has been found that the incidence of leukaemia among them has increased.

In Japan, the product was used from 1932 to 1945 for 10,000 to 20,000 patients, the majority of whom were injured in World War II. This follow-up examination program estimates the amount of thorium deposited in surviving patients, investigates their clinical symptoms, analyzes the relationship between the deposited amount and carcinogenesis, and elucidates the effects of long-term internal radiation exposure on human bodies. This year, the medical check-up was carried out for only one patient.

5) Database

Since radiation accidents requiring medical care are extremely rare, as much medical information as possible must be collected from each accident and accumulated to help medical professionals to making decisions for strategies to treat victims, and establish and improve therapeutic methods. A medical database including the cases of radiation exposure at Bikini Atoll in the South Pacific and cases of thorotrastosis is being constructed. Today, there are many database systems on radiation accidents and their victims, but most are only accessible from related countries. Under the supervision of the World Health Organization (WHO), an international program called REMPAN exchanges information on radiation accidents, including those in the database owned by the US REAC/TS (Radiation Emergency Assistance Center/Training Site). REMPAN has a collaborating center at Ulm University in Germany and manages a SEARCH database of patient information. It aims to construct an international database by registering cases that are attributable to the Chernobyl accident and other radiation accidents. NIRS registered the Daigo Fukuryu maru accident in the SEARCH database. In addition, our center is constructing a database by collecting medical data on the victims of radiation accidents and exchanging information with countries that have developed radiation accident medicines. In FY2007, medical data on treatment of internal contamination

with radionuclides were collected from the United Kingdom, Italy, Belgium, and Germany.

6) Special topics

a) Establishment of 24 hour emergency call system and telephone consultation for radiation effects system

For more than 10 years, NIRS has provided medical assistance to hospitals, radiation facilities, companies, and others. However, phone calls could not be answered at night, on weekends, or on national holidays, since a 24-hour call emergency system had not been established. In FY2007, NIRS established the 24-hour on-call emergency system for hospitals and first responders including fire departments. This the 24-hour on-call emergency system is for direct or consultative assistance regarding medical and health physics problems associated with radiation or nuclear accidents. After normal business hours, phone calls are automatically transferred to 3 or 4 staff members of the Research Center for Radiation Emergency Medicine at NIRS (who include a medical doctor and a health physicist).

NIRS has another telephone consultation assistance system. The number of phone calls for consultations on radiation effects is increasing. This year we received 76 consultations. Of those, 62 were consultations on radiation exposure. Nineteen cases were about exposure to radiation in medical use and 10 were accidental exposure. None of them needed medical care. However, there were a few cases with persons who believed that they had been exposed to radiation without evidence.

b) Physical Dosimetry and Chromosome Network Councils

To smoothly perform dose evaluation of the internal contamination by radionuclides in a radiation emergency, the in-vivo and in-vitro measurement system including internal dose evaluation code of each member organization was reviewed in the physical dosimetry network. While the measurement method and the equipment composition were various in each organization, it was confirmed that each organization can respond to radiation emergencies. As for the computer codes used, MONDAL which was developed by NIRS was highly evaluated. On the other hand, the "Livelink" solution which has been adopted by IAEA, was found to provide accurate information that was key in a radiation emergency. The validation methodology for feasibility study is being considered now. Agreement concerning cooperation in radiation emergencies will be obtained regarding internal exposure dose evaluation based on these results. This year, the investigation of WBCs was carried out at 6 radiation emergency hospitals of second level using standard BOMAB phantoms. There was a big difference in results of measurements depending on the kind of the phantom used when the manufacturer tested it. Among them, the best one was ±3% error from the standard but the worst one was -80%.

The chromosome analysis network was established after the JCO critically accident at Tokai-mura in 1999. The first version of a standard curve for dose estimation by chromosomes was established by the common criteria for dicentric analysis. This year, an exercise for the dose estimation by chromosomes was performed. NIRS sent two samples of radiated blood to collaborating laboratories. No information on the dose was provided. However, the estimated dose by each collaborating laboratory in the network was almost identical. The first consultation meeting for the establishment of international cytogenetic dosimetry network was held in Geneva Switzerland, December 17-18, 2007 by WHO. Two members from the biodosimetry section attended this meeting where the general scope and concept-of-operations framework were discussed for the establishment of a global biodosimetry laboratory network for radiation emergencies.

7) International Cooperation

a) Training courses for foreign medical staff organized by NIRS

Two training courses were held for medical professionals of Asia. From December 4 to 6, 2007, a training course for Taiwanese medical professionals on radiation emergency medical preparedness was held upon request and 26 persons attended from Taiwan. The Korean Institute of Radiological and Medical Sciences (KIRAMS) asked NIRS to provide a training course for Korean medical staff. From December 11 to 13, 2007, a training course for Korean medical professionals was held and 23 persons attended from Korea.

b) Organization of meetings

- 'NIRS/NSC Workshop on Medical Response to Nuclear Accidents in Asia' in collaboration with IAEA was organized at NIRS from January 30 to February 1, 2008. Two professionals from IAEA and 19 from China, India, Indonesia, Malaysia, Sri Lanka, South Korea, Pakistan, Philippines, Thailand, and Vietnam attended the workshop and discussed the network for radiation emergency medical preparedness in Asia.
- Special lecture by Dr. Bill McBride (from US) about research for treatment of high-dose exposure on 9 January 2008.
- Special lecture of Dr. Volker List (from Germany) about internal contamination with Pu on 9 January

2008.

c) Invited lectures

Our staff was invited to give lectures in the following meetings and training courses.

- International Symposium of "Emergent Medical Management of Radiation Accidents" held in Taipei, Taiwan from May 24 to 28, 2007.
- "The 6th Asia Pacific Burns Congress" held in Seoul, Korea from June 3 to 5, 2007.
- "KIRAMS regional exercise at KINS" held in Daejeon, Korea October 23, 2007.
- "BATAN-JAERI Joint Training Course on Radiological Emergency Preparedness and Response" held in Jakarta, Indonesia from October 28 to November 3, 2007 sponsored by the JAEA.
- IAEA/RCA Regional Training held in Daejeon, Korea from November 12 to 17, 2007
- "The 2nd Saudi International Conference on Military Medicine" held in Dhahran, Saudi Arabia from March 1 to 3, 2007.

d) International meetings / Conferences

NIRS staff attended the following meetings.

- IAEA/RCA meeting on "Sustainability of Regional Radiation Protection Infrastructure" held in Colombo, Sri Lanka from May 7 to 11, 2007.
- Consultants Meeting on " Overview of Radiotherapy Infrastructure Worldwide (DIRAC) " held in Vienna, Austria from June 12 to 15, 2007.
- "2nd Meeting of the Asian Nuclear Safety Network (ANSN) Topical Group on Emergency Preparedness and Response" held in Jakarta, Indonesia from June 10 to 14, 2007.
- International Joint Operations Command Conference 2007 held in Birmingham, UK from June 25 -26, 2007.
- IAEA/RCA Regulation Meeting held in Vienna, Austria from October 15-19, 2007.
- India-Japan specialists meeting held in Mumbai, India from November 13 to 15, 2007.
- IAEA/RCA (RAS/9/042) Asian ARALA Network Meeting held in Daejon, Korea from December 2 to 5, 2007
- WHO Information Gathering Concerning Treatment Method of Radiation Skin Trouble held in Geneva, Swiss from December 17 to 18, 2007.

e) Members of international committees

NIRS staff participated in the following comittees.

- WHO TMT Handbook Project : Consultancy Meeting on Work Package 4 (WHO) held in Geneva, Swiss from August 7-9, 2007.
- GHSAG (Global Health Security Action Group) Initiative/ Global Health Security Action Group held in Washington, USA from October 29 to November 2, 2007.
- Annual Meeting of International Commission on Radiation Units and Measurements (ICRU) held in Florence, Italy from October 10 to 14, 2007.

f) Other Visitors

- Upon a request from a hospital in Singapore, we accepted one medical staff member from September 23 to October 3, 2007 to see a domestic pre-hospital training course on emergency response for first responders held at NIRS. The participant learned about the system supporting nuclear disaster prevention drills in Japan.
- Three professionals from the National Institute for Radiological Protection, Chinese Center for Disease Control and Prevention (Chinese CDC) visited our facility to see a domestic pre-hospital training course on emergency response for first responders from November 26 to 28, 2007. In addition, we discussed a future cooperative project for radiation emergency medicine between NIRS and Chinese CDC, and we exchanged a memo of understanding.
- Four professionals from the Beijing Institute of Radiation Medicine visited our facility and discussed a future cooperative project for radiation emergency medicine with NIRS staff on December 17, 2007

6.1 The Study for Medical Treatment for High Dose Exposure

Makoto Akashi, M.D., Ph.D.
Director, Department of Radiation Emergency Medicine

Outline of Research Career

Dr. Akashi started his medical career at Jichi Medical School (Tochigi Prefecture) as a junior resident of internal medicine in 1981. He worked as a senior resident at the Division of Hematology of Jichi Medical School and moved to the division of hematology/oncology at UCLA School of Medicine in 1987. He received a Ph. D. from Jichi Medical School in 1988. He became a staff member of NIRS in 1990. His major works are: 1) Establishment of radiation emergency medical preparedness, 2) Research on radiation injuries, including molecular and cellular mechanisms, 3) Development of methods for mitigation of radiation injuries. He has treated patients of the criticality accident in Tokai-mura.

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Objectives

This group conducts studies that are usually not performed by other research institutions, emphasizing the diagnosis and treatment of radiation injuries due to high dose exposure. The group tries to clarify the mechanism of injuries in cells and tissues exposed to high doses of radiation and their effects on survival, repair, and maintenance of function. In this study, we evaluated candidate substances for therapeutic drugs particularly for gastrointestinal and skin injuries. For gastrointestinal injuries due to radiation, the group uses experimental animals, primary cultured cells, and tissues to develop quantitative evaluation systems. In addition, the groups studied medical treatment with cytokines, natural products, and synthetic compounds that decrease the severity of injury.

To develop accurate diagnostic dose assessment for high-dose exposure to radiation, this group also tries to find markers for radiation exposure from bio-molecules contained in samples which can be collected less invasively, such as blood. The group tries to determine genes, proteins, and other constituents of the living body that can provide a guide to treatment for radiation exposure.

Progress of Research

1) Study on treatment for skin injuries due to high doses of radiation

Ionizing radiation at high doses causes skin damages and hair loss, and apoptosis of hair follicles is one of the major prognostic factors. However, it is difficult to examine the skin and hair loss in small animals such as mice, because total body irradiation (TBI) causes their death with a very high dose. Therefore, we aimed to establish the in vivo assay system of radiation-induced apoptosis in plucking-induced anagen hair follicles and we used this assay to evaluate preventive effects of FGF1. A portion of the dorsal skin of seven-week-old male BALB/c mice harboring uniform telogen phase hair follicles was depilated for induction of anagen. BrdU incorporation and PCNA staining confirmed that the follicle keratinocytes were markedly proliferating at the following anagen phase. The mice received TBI with gamma-rays at doses from 8-16 Gy at anagen V 6 days after depilation. TUNEL assay was performed on paraffin-embedded sections of the dorsal skin to evaluate apoptosis over time after irradiation. The results in this study were as follows: (1) Radiation induced few instances of apoptosis in the non-depilated skin. (2) Radiation drastically increased apoptotic cells in the hair follicles of the depilated skin 8 to 24 h after irradiation. (3) It induced an active form of caspase 3-positive cells in the hair bulbs 8 h after irradiation. (4) It induced hair follicle dystrophy and regression from anagen to catagen in the follicles of the depilated skin in a radiation dose-dependent manner. (5) FGF1 significantly decreased the proportion of apoptotic cells in the hair follicles after irradiation.

Our findings revealed the induction of anagen by plucking the hairs was useful for evaluating the radiation-induced apoptosis, and it enables us to analyze a new substance for effects on radiation skin damage and hair loss in the mice irradiated at a lethal dose.

2) Inhibition of the ionizing radiation-induced activation of pro-death caspase-2 by a C-terminal PIDD (773-917) fragment

PIDD (p53-induced protein with a death domain) plays a critical role in the activation of caspase-2 to trigger DNA damage-induced apoptosis through the formation of a PIDDosome, which contains the adaptor protein RAIDD and caspase-2. PIDD also plays an essential role in DNA damage-induced activation of the antiapoptotic transcription factor NF-κB through the

formation of an alternative PIDDosome, consisting of PIDD, RIP1 and NEMO. Thus, PIDD acts as a molecular switch to turn life and death pathways on and off after DNA damage. We found that transcription of PIDD was induced after exposure of ionizing radiation in rat epithelial cell line (IEC6) cells, suggesting that PIDD might be a drug target for protection from ionizing radiation-induced gastrointestinal cell death. Yeast two-hybrid analysis indicated that the death domain of PIDD interacts with RAIDD. When a rat C-terminal PIDD fragment (residues 773-917) containing the death domain was overexpressed, it dominant-negatively inhibited the PIDD-mediated activation of caspase-2 after ionizing irradiation. In order to use the PIDD (773-917) fragment as an antiapoptotic drug, we purified a recombinant PIDD (773-917) fragment fused with 11-arginine which facilitates the uptake of the protein into mammalian cells with high efficiency.

3) The roles of TNFα in cells or mice exposed to radiation

Exposure to high dose radiation results in radiation injury that is a serious problem in accidental exposure and also in radiation therapy. Radiation activates the production of tumor necrosis factor α(TNFα) in various cells. However, the role of TNFα has not been fully understood in radiation exposure.

TNFα is one of the mediators of apoptosis. Previous studies have shown that TNFα expression is regulated by a transcription factor, early growth response-1 (Egr-1), in cell lines lacking p53. To better understand the pathways of TNFα expression after high dose irradiation, we used an inhibitor of MEK (PD98059), p38MAPK (SB203580) or PI3K (LY294002) and examined Egr-1 and TNFα expression in human T cell leukemia cell line Jurkat which lacks functional of p53. Studies of RT-PCR showed that the increased levels of Egr-1 and TNFα mRNA were observed immediately after 10 Gy irradiation ; the levels reached a plateau at 30 min. When Jurkat cells were pretreated with an inhibitor of MEK, or p38MAPK, and then irradiated at a dose of 10 Gy, both levels of Egr-1 and TNFα mRNA were reduced. Furthermore, when Jurkat cells were pretreated with an inhibitor of MEK, p38 MAPK or PI3K, radiation-induced activation of caspase-8 and caspase-3 was suppressed. In conclusion, our results suggest that ionizing radiation-induced TNFα induction is mediated by MEK, p38 MAPK or PI3K via Egr-1 induction in Jurkat cells. Further studies on mechanisms are in progress.

In this study, we also investigated the roles of TNFα in mice exposed to radiation. We compared the wild-type (wt) and the TNFα knock-out (k/o) BALB/c mice. Both groups of mice were subjected to γ-ray radiation. The survival durations in wt mice were significantly longer than those in k/o mice. Furthermore, exogenously added TNFα before radiation increased survival rate. We compared numbers of blood cells, and surviving intestinal crypts, apoptosis in crypt cells and activity of an antioxidant enzyme manganese superoxide dismutase (MnSOD) following radiation. There was no significant difference in numbers of white blood cells after exposure in the two groups. On day 15 after exposure, the numbers of red blood cells in wt mice was higher than those in k/o mice. Moreover, there was also no significant difference in numbers of surviving intestinal crypts after exposure and apoptosis in crypt cells between wt and k/o mice. Activities of MnSOD were lower in liver of k/o mice than that of wt mice. We also studied the expression of apoptosis-related proteins in mouse intestinal epithelial cells along the crypt-villus axis after radiation. The Bcl2 protein was constitutively expressed and its level was reduced by radiation in wt mice. In contrast, Bcl2 was not expressed in k/o mice and radiation did not induce its expression. Our results suggest that endogenously produced TNFα may play important roles in the radiation-induced injuries.

4) Lithium chloride reduces radiation-induced intestinal injury through inhibiting apoptosis in intestinal epithelial cells

High dose radiation induces apoptosis of intestinal epithelial cells and subsequent depletion of the stem cells, resulting in lethal gastro-intestinal injury. However, effective treatment of this injury has not been established yet. Lithium chloride (LiCl) is well known to activate a Wnt signal by inhibiting the activity of glycogen synthase kinase 3 (GSK3). The Wnt signal pathway has been shown to be associated with the maintenance of the stem cells of the intestinal crypt. Moreover, LiCl has been reported to inhibit neuronal apoptosis. The present study was designed to investigate effect of LiCl on intestinal injury induced by high dose radiation. Rat small intestinal epithelial cell line, IEC-6 cells and intestinal epithelial cells in primary culture obtained from 17.5 day fetal rat duodenum were used for in vitro assays. The cells were treated with LiCl 1 h either before or after γ-radiation of 20 Gy, and then cultured at 37°C until 24 h. The apoptosis was evaluated by Hoechst33258 staining of cells. Pretreatment with 10 mM of LiCl markedly inhibited radiation-induced apoptosis in IEC-6 cells. Addition of LiCl to these cells after radiation also blocked the apoptosis. The anti-apoptotic effect of LiCl was also found in intestinal epithelial cells in primary culture. Inhibition of either the phosphoinositide 3-kinase (PI3K) /Akt or mitogen-activated protein kinase (MAPK) /extracellular signal-regulated kinase (ERK) kinase (MEK/ERK) kinase pathway abrogated the anti-

apoptotic effect of LiCl. Western blot analyses showed that LiCl inhibited activation of caspase-3 and an induction of Bax in irradiated cells. Moreover, LiCl increased levels of Bcl-2 and Bcl-xL even in irradiated cells. We also administered LiCl to male Balb/c mice intraperitoneally an hour prior to TBI with 8 Gy. The numbers of crypts per circumference in jejunum were counted 3.5 days after TBI. The numbers of surviving crypts were greater in mice treated with 200 mg/kg body weight of LiCl than control mice with PBS. Thus, our results suggest that LiCl protects and rescues intestinal epithelial cells from radiation-induced apoptosis through activation of pathways involving PI3K/Akt and MEK/ERK. We also showed that LiCl reduced radiation-induced intestinal injury in vivo.

5) Study on the mechanisms of radioprotective effect of heat-killed Lactobacillus casei

Molecular mechanisms of the radioprotective effects of the natural substances and medicines in the mice were studied. Heat-killed ***Lactobacillus casei*** (LBC) showed strong radioprotective effect in C3H/He inbred mouse. Although no mice (n=110) survived 11.25 days in average after whole-body irradiation at supralethal dose (8.0 Gy) of X-rays, 28 day-survival rate reached 0.70 when the mice (n=100) were subcutaneouly injected with 30mg/kg of LBC 24 h before irradiation. Simultaneous administration of anti-inflammatory steroid, dexamethasone (Dex) reduced the survival rate to 0.37 (n=30). The reduction in the survival rate was not observed with the use of non-steroid anti-inflammatory drugs (NSAIDs), indometacin (0.80, n=30) nor sulpyrine (0.68, n=40). To reveal the effects of the LBC and Dex on the survival, we measured levels of an inflammatory cytokine, interleukin (IL) -1 beta in the circulation following the injection of LBC. Between 8 and 16 h after LBC-injection, the level of IL-1beta in blood reached maximam at 118 ng/mL (n=30) beyond the baseline level of less than 20 ng/mL. When the Dex was introduced with LBC, the maximal level declined to 40 ng/mL (n=12). The inhibition of the increase in the blood IL-1beta (IL-1β) levels by LBC was not observed when the indomethcin or sulpyrine were injected simultaneously. There results suggest that the radioprotective effect of LBC may be mediated by systemic inflammation reflected in the blood IL-1β levels. This also indicates the advantage of simultaneous use of NSAIDs for radioprotection due to their weak systemic effect on the inflammation.

6) Study on the effect of pharmaceutical agents on the recovery of intestine damaged by radiation

The aim of the study was to obtain basic data to choose favorable pharmaceutical agents against intestinal damage caused by accidental or therapeutic radiation. The intestinal damage in C3H/He inbred mouse was generated by single abdominal irradiation of a high dose of X-rays. Three to four days after the irradiation at a dose of more than 19.0 Gy, all the mice were emaciated with hematochezia and had decreased body weight, and finally died within 8 days, showing that intestinal damage contributed to their death. When the X-ray dose of 17.0 Gy was used and concomitant nutrient infusion was subcutaneouly injected once per day for 10 days, the body weights recovered to increase on Day 8 to 9 and mean survival rate of 0.60 (n=30) was obtained. Furthermore, we compared the effects of psychotropic agents in mice. Among minor tranquilizers, injection of phenobarbital did not cause significant change of the survival rate (0.53, n=15). In contrast, administration of a benzodiazepine derivative, diazepam drastically reduced the survival rate (0.23, n=20). This suggests several pharmaceutical agents may affect the recovery of intestine damaged due to radiation.

Major publications

1) H. Igaki, K. Nakagawa, H. Uozaki, M. Akahane, Y. Hosoi, F. Masashi, M. Kiyoshi, M. Akashi, K. Otomo, K. Maekawa : Pathological Changes in the Gastrointestinal Tract of a Heavily Radiation-exposed Worker at the Tokai-mura Criticality Accident, Journal of Radiation Research, 49, 55-62, 2007

2) K. Horie, E. Saito, V. W. Keng, R. Ikeda, H. Ishihara, J. Takeda: Retrotransposons Influence the Mouse Transcriptome : Implication for the Divergence of Genetic Traits, 176 (2), 815-827, 2007

6.2 Research on Radiation Dose Assessment for Radiation Emergency Medicine

Yuji Yamada, Ph.D.
Director, Department of Radiation Dosimetry

Outline of Research Career

Dr. Yamada received a Ph.D. from Nagoya University in 1989 for his study on collection performance of high efficiency particulate air filters. He has had 30 years of experience at NIRS in research on radioactive aerosols and their internal exposure at NIRS. Between 1986 and 1987 he was at the Inhalation Toxicology Research Institute (ITRI) of the Lovelace Foundation (USA) as a visiting scientist where he studied aerosol deposition within respiratory tracts.

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Objectives :

Radiation accidents can be divided into those resulting from external exposure and those resulting from internal exposure. For severe accidents, bone marrow transplantation may be considered depending on the external exposure dose received, or drug administration may also be considered to inhibit deposition and promote excretion of radioactive substances incorporated into the body. Dose assessment of victims in radiation accidents must be made within a short time in combination with the details of the accident to estimate the radiation effects and to initiate appropriate medical treatment.

Major subjects in radiation dose assessment research are 1) collection and analysis of information on the occurrence of radiation accidents, radiation type, and radioactivity ; 2) determination and evaluation of the amount of radioactivity in the body and excreta ; and 3) biological evaluation of the effects resulting from exposure on the body. Our aims are to shorten the time needed for analysis and dose determination, and to improve the accuracy of comprehensive assessment, which combines physical and biological dose assessments.

In the area of radiation emergency medicine, we have made basic and application studies for clinical use of agents in removing radionuclides, especially alpha emitters like plutonium or uranium that are incorporated into the body.

Progress of Research

1) Development of ESR dosimety using human nail clippings

Electron spin resonance (ESR) dosimetry is a method to measure radical numbers produced by radiation in substances and to estimate external exposure dose. This method is useful for dose estimations when workers are exposed while not wearing personal monitors and when the general public is exposed accidentally. Tooth enamel is typically used for this purpose. However, teeth cannot be extracted easily from the exposed persons in all cases. It is necessary to find other human tissues or substances around exposed persons for estimating personal exposures. Nail clipping samples are easily obtained from exposed persons compared with tooth enamel samples. Therefore, nail samples were applied to ESR dosimetry in the case of γ-irradiation. The relationship between ESR sensitivity and absorbed dose (Gy) in the nails was found to be linear. An unknown dose of γ -exposed nail was estimated in 3-4 weeks using the modified calibration curve at room temperature. For radiation emergency purposes, the analysis time was succeeded to shorten 3 times by increasing the ambient temperature to 50℃. Several problems must be solved to establish nail ESR dosimetry and we are working on their solutions.

2) Chromosome aberration analysis

In order to confirm the calibration curve for cytogenetic dosimetry, we analyzed the dicentric chromosome in human lymphocytes irradiated at doses of 0, 0.5, 1.0, 2.0, 3.0, 4.0, and 5.0Gy. The frequencies of dicentric chromosome occurrence at each dose point in these analyses were almost identical with those previously obtained by other investigators. This means that the quality level for the dicentric chromosome assay has not gone down. In the process of dose estimation by dicentric chromosome analysis, preservation of the blood sample may have a profound effect on the frequency of chromosome abnormality. Therefore, in the present study, we have begun analysis of the relationship between the dicentric chromosome frequency and temperature (4, 20 and 30°C) for preservation and also of checking the effect of higher concentration of Colcemid in human

peripheral lymphocytes. We expect results will be obtained in the near future.

Furthermore, in order to establish an assay system to evaluate the dose of partial body exposure, we used the human hair root as the target organ and detected indicators of dose estimation. We have also examined the method of culturing hair root cells for detecting chromosomal aberrations. The epilated hairs were dissected carefully, and single cells were isolated by enzyme treatment. When the hair was irradiated with γ-radiation, DNA damage was detectable in the comet assay, and the cultured hair root cells could be grown *in vitro*. These results suggest that dose estimation of partial body exposure may be possible using hair root cells.

3) Surface contamination monitor for unknown nuclides

When a patient is accepted at a treatment facility, surface contamination monitoring is carried out with more than one survey meter by reason of detecting multiple kinds of radiation in radiation emergency medicine. When internal contamination is doubtful, rapid deployment becomes possible if unknown nuclides can be identified at this stage. So development of an instrument which can distinguish all kinds of radiation with one detector was targeted to evaluate unknown nuclides promptly in the emergency locale. Different scintillators were adopted for detecting each kind of radiation such as a ZnS (Ag) scintillator for α-rays, a plastic scintillator for β-rays and a CsI (Tl) scintillator for γ-rays. These scintillators are optically coupled on the same axis and the scintillation light is detected by one photomultiplier tube. Here, α and β detectors are surrounded by a γ detector which also acts as a veto detector to reduce the contribution of environmental γ-rays to the other detectors. The principle of this instrument is the same as that of a Phoswich detector using the decay time difference of each scintillator. Namely, identification of three components from the plastic scintillator (decay time : 1.8ns), ZnS (Ag) (200ns) and CsI (1000ns), can be a trigger signal for each radiation measurement. The detection efficiency is equal to or higher than that of present commercially available survey meters. As a result, when a patient was contaminated by unknown nuclides, we confirmed that separate measurements of α-rays, β-rays, γ-rays made the identification of the nuclides possible.

4) Nasal swab for α emitters

It is effective to obtain useful information from the nasal swab sample for prompt internal dose estimation of α-particle emitting nuclides. Sample activity has generally been measured using gross α counters such as a ZnS (Ag) scintillation counter because their measurements are sufficient to judge intake of α-particle emitting nuclide has occurred. In order to obtain more information for emergency medicine, the measuring method using α spectrometry has been re-examined. Simulated nasal swab samples were prepared. A suspended solution of plutonium oxide (PuO_2 suspension) or a solution of plutonium nitrate ($Pu(NO_3)_4$ solution) was dropped onto a filter paper as a simulated nasal swab sample. The PuO_2 suspension and $Pu(NO_3)_4$ solution were assumed to simulate dust and mist exposure, respectively. The measured α spectra had a different shape for the PuO_2 suspension and $Pu(NO_3)_4$ solution. The spectrum of PuO_2 suspension had clear energy peaks. The peak energy showed no energy loss to the filter paper fibers. These results suggested that identification of nuclides would be easy using energy peaks even for mixed nuclide exposure. On the other hand, the spectrum of $Pu(NO_3)_4$ solution had unclear energy peaks. Almost the same count continued down to the lowest energy and because the solution infiltrated the filter paper fibers, the energy loss by them was large. We thought that this was the reason why the detection efficiency was lowered compared with the simulated dust exposure. These results suggested that α spectrometry would give useful information to estimate internal dose assessment.

5) Development of lung phantom for *in vivo* measurements and improvement of thyroid monitor

A thorax model had been designed and made to give a realistic shape of the lungs and Japanese body size. In FY2007, the model's composition and the distribution of the radioactivity were examined in detail. The material distribution in the model was confirmed by the X-ray tomography and by its actual cutting. Also a non-radioactive lung model, which was made in a similar way to the radioactive lung model, was cut and the composition analysis was done in several places. The result showed that the composition was almost the same, independent of the position. Therefore, the material distribution and the composition were proven to be uniform. Hydrogen, carbon, nitrogen, oxygen, and calcium accounted for 99% of the composition. The lung models were made by uniformly diffusing a radioactive-source in the polyurethane. Because the radioactivity was about 4.3kBq for a whole lung model, the sections of the radioactive lung model were closely set on the imaging plate inside a blackout-curtained area inside a low background room. The 59.5keV γ-rays from ^{241}Am were observed. Moreover, the mapping measurement was done that rolled the collimator of the lead 1mm in one-inch NaI detector. The obtained results confirmed the uniformity of the radiation source as well as the physical structure.

To improve accuracy of the thyroid monitor used at the site of a nuclear accident which is anticipated to release radioactive iodine to the environment, we developed a trial portable thyroid monitor that combined a Compton suppressor with high purity Ge detector. Its basic properties were measured under the optimized conditions at the maximum BG compensation. As a result, we confirmed that the monitor had a performance equal to that of heavy conventional thyroid monitor (detection limit: approx. 13Bq) with a lead shield. Good portability was also obtained.

6) Rapid technique for urine analysis

Bioassays are important method to estimate amounts of radionuclides taken into a human body in the event of a radiation accident that involves internal exposure, especially exposure by α-and/or β-emitters. In the case of internal exposure by soluble radionuclides, urine is used as a sample for bioassays and coprecipitation is mainly used to efficiently collect radionuclides from urine. However, on coprecipitation, it is difficult to estimate exposed dose quickly after a radiation accident happens, since with coprecipitation a lot of sequential chemical procedures must be followed. Then, we have developed a rapid coprecipitation method using a filtrating kit which is commercially supplied by Millipore Co. Nitric solution which mainly contains ^{239}Pu was used as a sample and the radioactivity was measured with a liquid scintillation counter and a high-purity germanium detector (HP Ge). Coprecipitation was completed within 2 h for a 400mL urine sample and soluble radionuclides were collected at the rate of more than 80% from the urine. Detection limits of exposed dose were estimated as 0.06Sv for inhalation and 0.02Sv for ingestion. The time needed for radiation measurements was about 1 h. From these results, it seemed possible to estimate the amounts of soluble radionuclides within 3 h after a urine sample was obtained.

7) Decision of detector efficiency in α-spectrometry by ICP-MS

Internal dose estimation due to α- and β-emitters has a difficulty compared with that of γ-emitters. For this purpose, chemical analyses of urine and feces (bioassays) are conducted to estimate the input and accumulated volumes of radioactive nuclides in a human body. After chemical separation, the final detection of α-emitter nuclides is usually by α spectrometer, ZnS-scintillator and ICP-MS. In all case, detection efficiencies of the methods are important to get reliable results. Detection efficiency of α spectrometry usually is determined by standard electro-coated sources. There sometimes is a difficulty to buy the source preparation. In this study, detection efficiency of α spectrometry was decided by using ICP-MS. Uranium-238 concentrations in all steps of electro-deposition (initial sample solution, remaining sample solution after electro-deposition) were determined by ICP-MS. Counts of an electro-coated source was also measured by α spectrometry. The detection efficiency calculated by two measurements (ICP-MS and α spectrometry) was identical to that by a standard source (^{241}Am). Detection efficiency could be estimated by ICP-MS, especially in radionuclides having a long-life.

8) Dose calculation from internal exposure

The PC software MONDAL3 has been released for non-specialists users to estimate the committed effective dose from an internal radiation exposure using the results of individual monitoring measurements. Preparations for a database update were made on the basis of a human alimentary tract model for radiological protection published as ICRP Publication 100. Also, the dose calculation for radioactive zinc was carried out for the salivary glands and male reproductive organs. These organs were not included as source organs in the ICRP biokinetic model of Zn, though experiments in rats show relatively high Zn concentrations. The numbers of disintegrations in the testes, the prostate gland, salivary glands and the thymus were calculated from experimental results in rats, and SAFs (specific absorbed fractions) from the MIRD stylized model were determined under some assumptions. The equivalent dose of the testes or the prostate gland may be about ten times higher than the dose of the rest of the body. On the other hand, the dose of the salivary glands or thymus which showed a high density temporarily but rapidly decreased, may compare with that of other organs.

9) Acute toxicity of uranium and the effects of chelating agents in simulated wounds using rat model

The study focused on (1) the examination of the acute toxicity of uranium induced by uranium-contaminated wounds, and (2) the effects of chelating agent CBMIDA in local treatment of these wounds.

To clarify the differences in behavior and toxicity at different depth of wounds that depleted uranium (DU) initially entered, different doses and chemical forms of uranium (4 and 16 mg/kg DU in pH=1 or pH=7 solutions) were administered by intracutaneous (IC), subcutaneous (SC), and intramuscular, and intraperitoneal injections to four groups. Uranium (pH=1) injected as IC and SC was retained at a level of about 60-70 % in the injected sites for 1-3 h, 76～96% excreted at 24h, and the rest was deposited in liver, kidney and femur; their biochemical markers increased significantly 1 h. Uranium excretion was time-

dependent in urine and feces and digestive duct, and dependence was greater in feces more than in urine.

CBMIDA was infused into the wounds 0, 10, 30, 60, 120 min and 24 h after DU injection. The results indicated that CBMIDA could decrease uranium in the DU injected sites, kidneys, and femur, as well as the serum creatinine and urinary NAG/creatinine, and CBMIDA accelerated excretions of uranium in urine and feces when it was administered 30-120 min after DU injection.

7. Fundamental Technology Center

Yoshikazu Nishimura, D.V. M., Ph. D.,
Director, Fundamental Technology Center

Outline of Research Career

Dr Nishimura received a Ph. D. from the University of Tokyo in 1984 for his study on the biokinetics of radiocobalt in rats. He has 30 years of experience in research on biokinetics of radionuclides in experimental animals. He has also studied how to reduce radionuclide concentrations in animals and humans using natural chelating agents such as chitin and chitosan. He was a group leader of the Environmental Radiation Protection Research Group from 2005 to 2006. Since April 2006 he has been Director of the Fundamental Technology Center.

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Overview

The Fundamental Technology Center performs advanced research and development necessary to support the activities of NIRS. It manufactures major pieces of research equipment for the Institute and ensures the safety of laboratory apparatuses. The Center consists of one office, tow departments and seven sections (Fig. 13). The Planning and Promotion Office is responsible for planning and promotion of work in the Center, and it promotes common use facilities. The Office sponsors technical meetings to combine and improve the technical foundations of NIRS.

The Department of Technical Support and Development consists of three sections: (1) Technical advancement of radiation systems section; (2) Radiation measurement research section; and (3) Laboratory animal sciences section. The Department of Safety and Facility Management consists of four sections: (1) Radiation safety section; (2) Specific laboratory management section; (3) Safety control section; and (4) Facility management section. This department promotes improvements in: (1) the handling of radioactive substances and nuclear materials; (2) safety measures used in the control of radiation generators such as HIMAC; (3) control of radioactive wastes and dangerous substances; and (4) safety of the working environment for NIRS employees. It also maintains the facilities and equipment necessary for safety assurance. This department has instituted the plan for the facilities and equipment to be set up and used over the next 10 years and it now implements the effective use of the facilities and equipment over the planned timeframe.

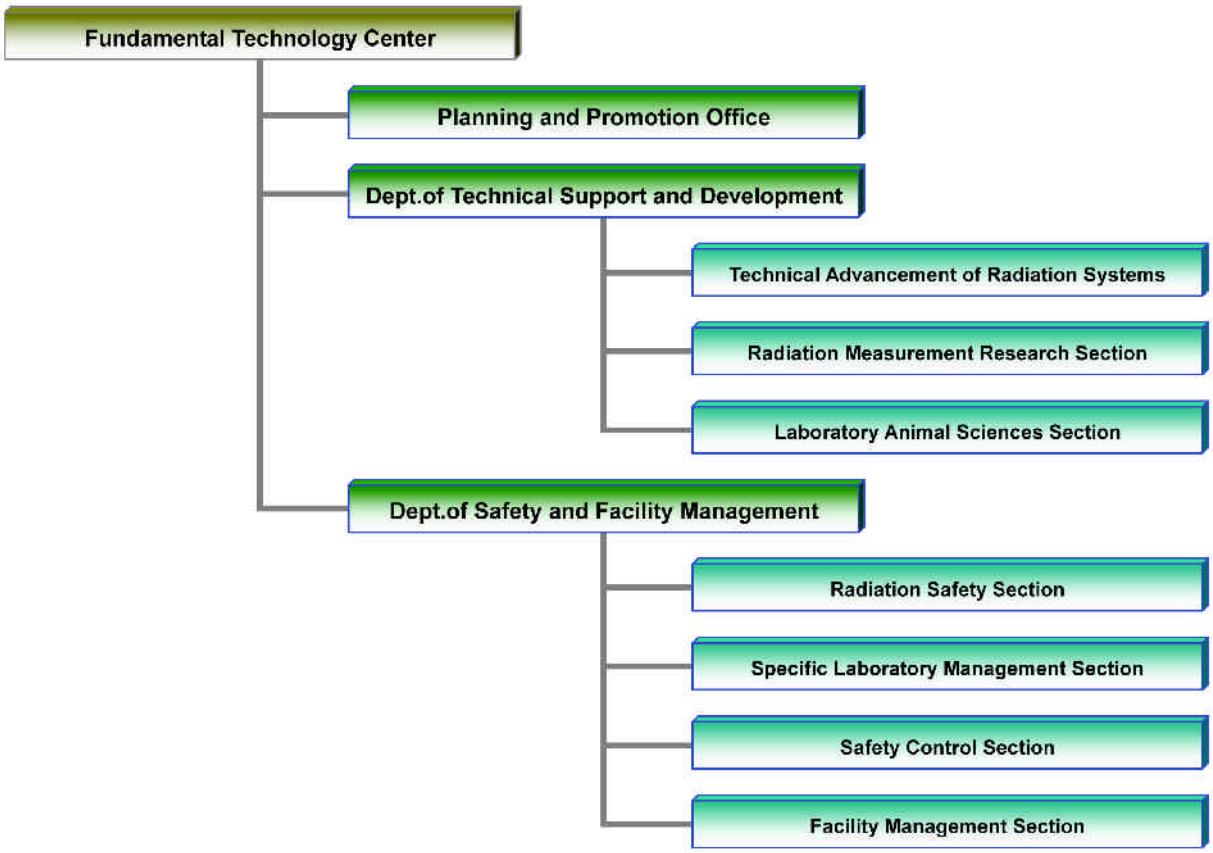

Fig. 13. Organization of Fundamental Technology Center

7.1. Study of Radiation Measurements

Yukio Uchihori, Ph.D.
Senior Researcher, the Radiation Measurement Research Section

Outline of Research Career

Dr. Uchihori received a Ph.D. from Osaka City University in 1995 for his study on cosmic-ray physics at a high mountain and deep underground. He joined extremely high energy cosmic-ray experiments as a fellow in Institute for Cosmic Ray Research, Tokyo University. In 1996, he moved to NIRS and worked on space radiation protection and measurement. He worked in the MEXT (Ministry of Education, Culture, Sports, Science and Technology) in FY 2006 and in the planning section in NIRS.

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Objectives

NIRS Researchers in radiation biology and physics need reliable dosimetery or measurement data in the radiation field. The Radiation Measurement Research Section supports their activities using both conventional and the latest radiation detectors. Section members also propose research topics in new radiation fields like micro-beam and low dose neutron facilities to NIRS biologists and physicists.

Several detectors have been developed using leading-edge techniques and calibrated in various radiation fields like HIMAC, cyclotrons, neutron fields, and so on. Not only detectors themselves but also analysis methods including hardware, software, and simulation codes, and electronics have been developed.

Dosimetery of space radiation is another research objective and several detectors for space radiation measurements were developed. In collaboration with the Institute of Bio-Medical Problems (IBMP), Russian Academy of Science, there were several opportunities to measure space radiation in the International Space Station (ISS). Also, an international intercomparison program of space radiation detectors, the ICCHIBAN (InterComparison for Cosmic-rays with Heavy Ion Beams At NIRS) Project, continues to understand and standardize detectors for space radiation dosimetery.

Progress of Research

1) Passive detectors (Nakahiro Yasuda, Iva Jadrnickova)

a) Development of the fluorescent nuclear track detector technique

A new optical, non-destructive method of detecting and imaging individual heavy charged particle tracks using fluorescent nuclear track detectors (FNTDs) is being investigated as a possible spectroscopic technology for heavy charged particles of low and high linear energy transfer (LET). The technique uses new luminescent aluminum oxide single crystals having aggregate oxygen vacancy defects and doping with Mg (Al_2O_3 : C, Mg) in combination with laser scanning confocal fluorescence microscopy. Major advantages of Al_2O_3:C, Mg FNTD over conventionally processed CR-39 plastic nuclear track detectors include superior spatial resolution, a wider range of LET sensitivity, no need for post-irradiation chemical processing of the detector and the capability to anneal and reuse the detector. Spectroscopic capabilities of this new method were demonstrated for energetic heavy ions of LET$_\infty$$H_2O$ ranging from 2 to 8700 keV/μm. The new technology is intended for use in neutron detection and dosimetry, proton and heavy ion radiobiology, and space radiation dosimetry as well as in nuclear and particle physics research.

b) Polyvinyltoluene scintillators for relative ion dosimetry

We have developed a dosimeter prototype, devoted to ion beam dosimetry, and tested it with helium, carbon and neon ions having an equivalent range in water of 150 mm. A polyvinyltoluene-based plastic scintillator is used to convert the deposited energy into scintillator ; a measurement probe and a long optical fiber guide the light to a photon counting unit. Using 10 - 40 μm thick scintillators, we showed that the dosimeter gain is enough to provide useful measurements. The ion-induced scintillation can be interpreted using a model taking into account the energy deposited by secondary electrons. For practical purposes, it was shown that a linear relationship can be established between the scintillation signal and the relative dose.

c) Gold deposition development method for a nuclear emulsion in charged particle detection

The gold deposition development method instead

of the normal development method was applied to a nuclear track detector by using silver halide photography. Fine tracks formed by spherical gold grains were observed without any filaments. The grain size does not depend on the initial size of the silver halide crystals but only on the deposition period. This implies that the grain size can be adjusted to a size similar to the resolving power of an optical microscope in spite of the use of an ultra-fine crystal emulsion. As a consequence, charge resolution becomes higher compare to traditional silver halide photography. In addition, the developer used in the gold deposition method does not contain harmful organic reagents, and it contains a lower amount of inorganic salts than normal developers. The solution can be safely handled and the disposal treatment of the solution is easy.

d) Determination of dosimetric and microdosimetric characteristics onboard the ISS

Cosmic radiation represents an important health risk for astronauts. To estimate the radiation onboard spacecraft, it is necessary to obtain the data on dose distribution under real space flight conditions at various locations in the spacecraft. Several measurements were performed in the Russian Service Module onboard the ISS from 2004 to 2006. Usually, the combination of TLDs and track etch detectors (TEDs) is used to obtain total values of absorbed dose and dose equivalent ; TLDs are for the measurement of low-LET radiation dose, and TEDs determine the LET spectra of particle fluxes and measure the dose and dose equivalent from high-LET radiation (above 5 keV/μm). We have studied the variation of dose quantities and LET spectra in various compartments of the Service Module and on the surface as well as in a tissue-equivalent spherical phantom. The absorbed dose, dose equivalent, and quality factor as well as the contribution of low-LET and high-LET components of the radiation vary with the position of the detector ; the differences were observed to be up to factor of 2. During the evaluation of the detectors we also obtained additional, new results related to evaluation of TEDs that could be important especially for some inter-comparison of results measured with TEDs.

2) Neutron detectors (Masashi Takada)

Neutron detectors have to discriminate neutrons from γ-rays because γ-rays contaminated neutron fields. Liquid scintillators have been used to measure fast neutrons ; however, it is difficult to handle the detectors due to the use of xylene-based scintillators. Here, the characterization of pulse shapes of plastic scintillators, which are used normally for radiation measurements, has been studied. Pulse shapes of incident charged particles were measured at HIMAC and the NIRS cyclotron facility. Signals from 3 mm thick plastic scintillators detecting heavy charged particles were measured using a new data acquisition unit with 12-bit FADC and 500 MHz sampling speed. For the signal measurements, particle species, incident energies and applied high voltages were varied to find pulse-shape dependence on incident particles. Signal-charge ratio of the signal tail to peak was observed to be dependent on deposited energy in the scintillators ; however, the ratio dependences were also dependent on applied voltage. Next, it is planned to analyze pulse shapes will be analyzed to find the possibility of particle identification using a plastic scintillator.

3) Scintillation detector (Hidehito Nakamura)

The improvement of sensitivity in clinical PET/SPECT imaging should lead to reductions in injected dose of radiopharmaceuticals and acquisition time. CROSS (Correlation Response Observatory for Scintillation Signals) aims to realize high sensitivity, i. e., high signal-to-noise (SN) ratio, high energy, time and position resolution, by building an organic scintillator as the main component into the clinical SPECT/PET scanner.

The CROSS-mini as a test module was developed to archive high sensitivity (Fig. 14). A plastic scintillator plate as an organic scintillator and two NaI(Tl) plates as an inorganic scintillators are adopted in the CROSS-mini. Each plate is 62 × 62 × 10 mm^3. The plastic scintillator plate (BC-408) is provided by Saint Gobain. The NaI(Tl) plates were newly developed by OKEN and NIRS. The top and bottom large surfaces of each plate are coated with laminated aluminum (100 nm in thickness) to reflect scintillation photons. The scintillation photons can be measured on the other 4 sides. The CROSS-mini is configured by interlaminating the plastic scintillator plate and the NaI(Tl) plate at each coated surface.

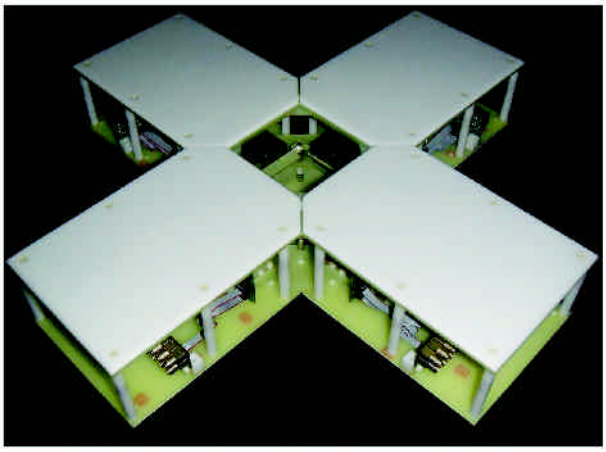

Fig. 14. Photograph of CROSS-mini. The data acquisition system by ASIC and FPGA is mounted into CROSS-mini.

4) ICCHIBAN program (Yukio Uchihori, Nakahiro Yasuda, Hisashi Kitamura)

Within the ICCHIBAN project, the 2nd Space-Intercomparison experiment was carried out at the Russian Service Module in the ISS in collaboration with IBMP. Passive detectors (e. g. thermo luminescent detectors (TLDs), optical simulated luminescent detectors (OSLs), and track-etch detectors (CR-39)), for space radiation work at 13 institutes and universities in 10 countries were sent to NIRS and packed in an aluminum box (Fig. 15). The box was launched as Russian Progress Space Cargo and attached on a wall in the ISS for 6 months. It was later returned to earth by a Russian Soyuz Space Ship and dismantled. The detectors in the box were delivered to their participants and analyzed by them. The data will now be gathered by NIRS and discussed in an international workshop in the near future. This project helps us to compare their detectors from various institutes and to understand the space radiation field in the ISS. The results will support not only Japanese space activities but also astronauts' and cosmonauts' activities from other countries as well.

Fig. 15. Photograph of a detector package in the Space-Intercomparison experiment.

Major Publications

1) M. Akselrod, E. Benton, N. Yasuda et al., Nucl. Inst. and Meth. B247, 295-306, 2006
2) D. Broggio, R. Barillon, N. Yasuda et al., Nucl. Inst. and Meth. B254, 3-9, 2007
3) K. Kuge, N. Yasuda, H. Shibuya et al., Radiat. Meas. 42, 1335-1341, 2007
4) M. Takada, T. Nakamura, Rad. Prot. Dos. 126,178-184, 2007
5) H. Nakamura, H. Ejiri H. Imaseki et al., J. Phys. Soc. Jpn. 76,114201-1-114201-9, 2007

8. List of Original Papers

This list includes main publications by the staff members issued during the period from April 1, 2007 to March 31, 2007

* Outside Co-research

Research Center for Charged Particle Therapy

Developing Advanced Clinical Therapy with Charged Particle

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Sadayo Saito, Chief Nurse
Kiyoko Tahara, Chief Nurse
Yoko Yamasita, Chief Nurse
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Shin Watanabe, Head and 1 staff
Radiological Technology Section
Kazuhiro Watanabe , Head and 11 staffs

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Mitsutaka Kanazawa, Ph. D.
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Yukio Kamakura, Deputy Director

Planning Section

Shin-ichiro Sato, M. D., Ph. D., Head

Yoshihito Watanabe, Ph. D., Senior Specialist

Masashi Sagara, Ph. D., Senior Specialist

Takashi Fujita, Senior Specialist [1)]

Yukio Uchihori, Ph. D., Senior Specialist

and 5 staffs

Intellectual Property Section

Yukio Kamakura, Head [1)]

and 3 staffs

International and Research Cooperation Section

Sadayuki Ban, D. M. Sc., Ph. D., Head

and 5 staffs

Training School Section

Yoshiyuki Shirakawa, Ph. D., Head

and 4 staffs