The Proceedings of The 2nd international Symposium on Radiation Emergency Medicine at Hirosaki University

The 2010
Hirosaki University
International Symposium

The 2nd International Symposium on Radiation Emergency Medicine at Hirosaki University

Organizer: Hirosaki University Graduate School of Health Sciences
Sponsors: Aomori Prefecture, Hirosaki City

PREFACE

Since its project on radiation emergency medicine was initiated three years ago, Hirosaki University Graduate School of Health Sciences has worked to create an advanced professional education program in this field. Based on the University's established education philosophy and objective, the curriculum for postgraduate as well as entry-level undergraduate education in the School of Health Sciences has undergone extensive development during this period, and the new education program commenced in April of this year. The mission of this project is to improve the quality of education and to promote research based on the development of human resources in health professionals, particularly in the field of radiation emergency medicine.

In line with these initiatives, the 1st International Symposium on Radiation Emergency Medicine at Hirosaki University was held on August 1st 2009, under the theme of "Basic Research on Radiation Sciences and Radiation Emergency Medicine". Recently, the executive committee was making preparations to host the 2nd International Symposium at Hirosaki University on 10 October 2010. The focus of the 2nd International Symposium was the missions and challenges of health professionals in radiation emergency medicine. Major topics included the current status of and past clinical experiences in nursing, medical technology, and rehabilitation as related to radiation emergency medicine. The 2nd International Symposium placed a particularly strong emphasis on interdisciplinary studies and discussion of the future directions of this field.

Distinguished guests from France were invited to the Symposium, and lectures and discussions were held concerning radiation emergency medicine. Presentations comprised four sessions, and 24 speakers lectured on topics related to their current research. Participants were deeply impressed by the special guest speakers and the Symposium was highly successful in promoting the exchange of recent, new developments in this field. This report summarizes the presentations and discussions held at the Symposium.

We would like to acknowledge the contributions of the guest speakers and the members of the governing board of the Symposium, who made what I hope to be the first of many successful meetings run smoothly.

Hitoshi Tsushima
Chief Chair, The 2nd International Symposium on Radiation Emergency Medicine at Hirosaki University
Dean of Graduate School of Health Sciences, Hirosaki University

Symposium

Opening by Professor Hitoshi Tsusima,Dean of Hirosaki University Graduate School of Health Sciences, Chair of Symposium I , The 1st presenter

Professor Toshiya Nakamura,Hirosaki University The 2nd presenter

Professor Kazuharu Nishizawa,Hirosaki University The 3rd presenter

Professor Yoko Saito,Hirosaki University The 4th presenter

Professor Manabu Iwata,Hirosaki University Chair of Symposium II

Dr Masahiko Kimura instead of reading Proferssor Hideharu Tanaka, Kokushikan University The 5th presenter

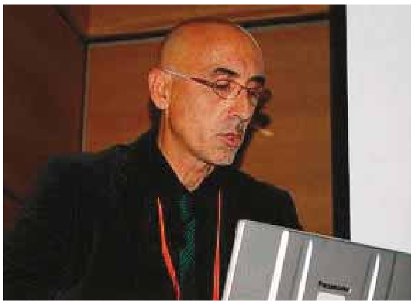
Chief Nurse Yoko Yamashita,NIRS The 6th presenter

Dr Masahiko Kimura, Kitasato University The 7th presenter

Professor Hideki Yamabe,Hirosaki University Chair of SymposiumⅣ

Dr.Jean-Christophe Amabile, Service de protection radiologique des armies The 8th presenter

Pr.Pierre Laroche, Service de protection radiologique des armies The 9th presenter



Pr.Eric Lapeyre, Hopital d'Instruction des Armees Percy The final presenter

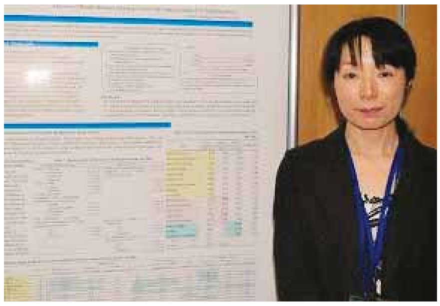

Professor Yoshiko Nihizawa,Hirosaki University Poster presentation 1

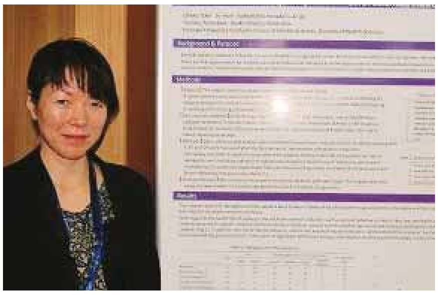

Associate professor Chiaki Kitamiya,Hirosaki University Poster presentation 2

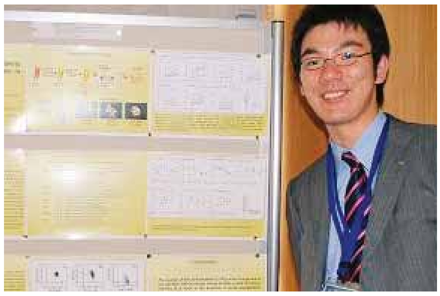

Aassistant professor Shuhei Koeda,Hirosaki University Poster presentation 3

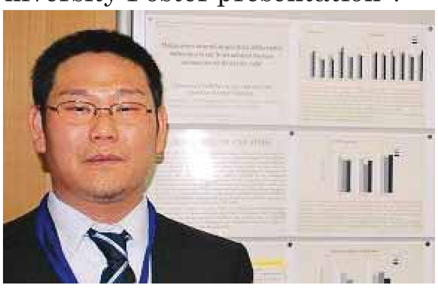

Professor Saichi Wakayama,Hirosaki University Poster presentation 4


Associate professor Ruriko Kidachi,Hirosaki University Poster presentation 5


Associate professor Yuka Noto,Hirosaki University Poster presentation 6


Associate professor Chieko Itaki,Hirosaki University Poster presentation 7


Aassistant professor Monzen Satoru,Hirosaki University Poster presentation 8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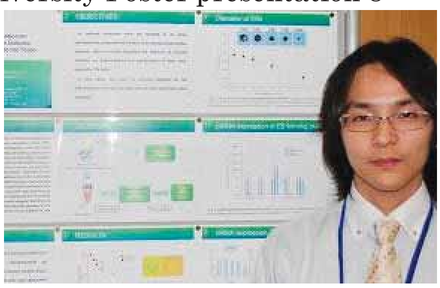
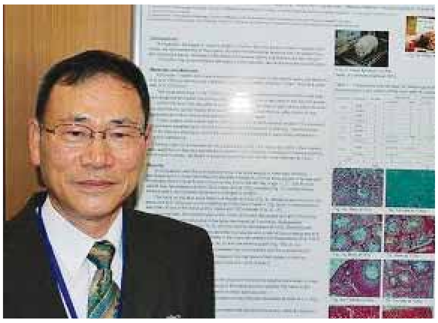
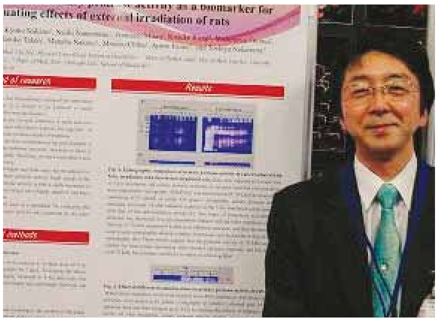
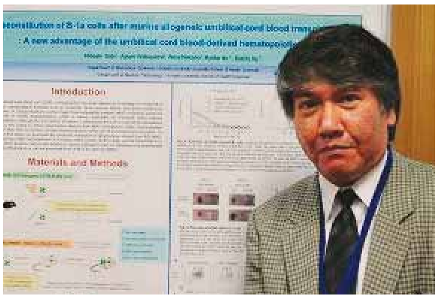

Doctoral Course Naoki Hayashi,Hirosaki University Poster presentation 10



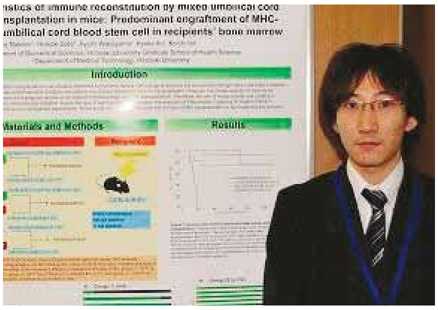
Professor Shoji Chiba,Hirosaki University Poster presentation 11



Lecture Takashi Ishikawa,Hirosaki University Poster presentation 12

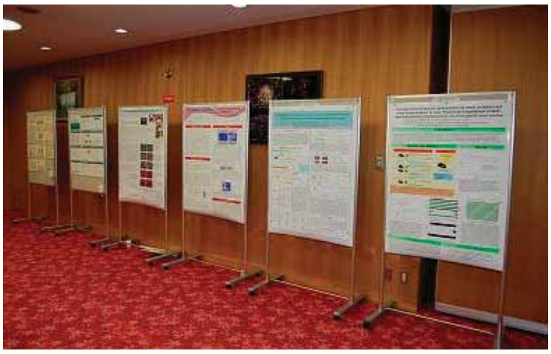


Associate professor Koichi Ito,Hirosaki University Poster presentation 13



Doctoral Course Akira Nakano,Hirosaki University Poster presentation 14

Closing by Professor Kazuyuki Kida,Deputy Head of Hirosaki University Graduate School of Health Sciences




The 2nd International Symposium on Radiation Emergency Medicine in Hirosaki University
- Missions and Challenges of Health Professionals in Radiation Emergency Medicine -
Hirosaki University Graduate School of Health Sciences

Welcome Reception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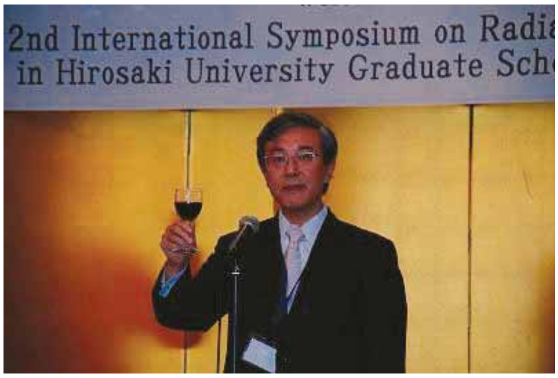
2nd International Symposium on Radi
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Contents

Symposium Ⅳ

Poster Session（Symposium Ⅲ）

Developing health human resources for radiation emergency medicine at Hirosaki University; educational philosophy and objectives.

Hitoshi Tsushima*

Dean of Hirosaki University Graduate School of Health Sciences

Introduction

Although careful attention is paid to the safe use of radiation, and appropriate radiation protection measures are taken, the probability of a radiation exposure accident is not zero. When an accident occurs, either a nuclear disaster or a radiation accident, it has a great influence on peripheral people and the community as well as on the worker of the institution. Especially, occurrence of health damage to a human body is the most serious problem. Therefore, as a precaution against unlikely accident occurrence, it is an indispensable problem not only to maintain a system for radiation emergency medicine but to prevent similar incidents. Against such a background, Hirosaki University Graduate School of Health Sciences has been working on the development of health human resources for Radiation Emergency Medicine since 2008. In this article, a brief summary of our project and educational philosophy and objectives as a mainstay of human resources development were described.

The radiation emergency system in Japan

In Japan, the 19 prefectures where nuclear facilities are located or nearby are divided into eastern and western divisions. The radiation emergency system is organized around the National Institute of Radiological Sciences and Hiroshima University, which are designated as the "local tertiary radiation emergency hospitals" for those divisions, respectively (Fig1.). Consolidating advanced medical technologies is indispensable for radiation emergency medicine. In addition, specific countermeasures, such as nursing for patients exposed to radiation, measures for contamination control, decontamination, radiation dosimetry, and specified clinical assays, are required. Nevertheless, the radiological content of current medical education is included within the general curriculum. Thus, a special educational program is required to deal with radiation emergency medicine. In Aomori, many atomic energy-related institutions are located. And Hirosaki University hospital has a role as the local tertiary radiation emergency hospitals specified by Aomori prefecture government (Fig.2). The mission of Hirosaki University on radiation emergency medicine is to make up the system for receiving heavily exposed patients in Aomori, and to develop human resources in the field of radiation emergency medicine.

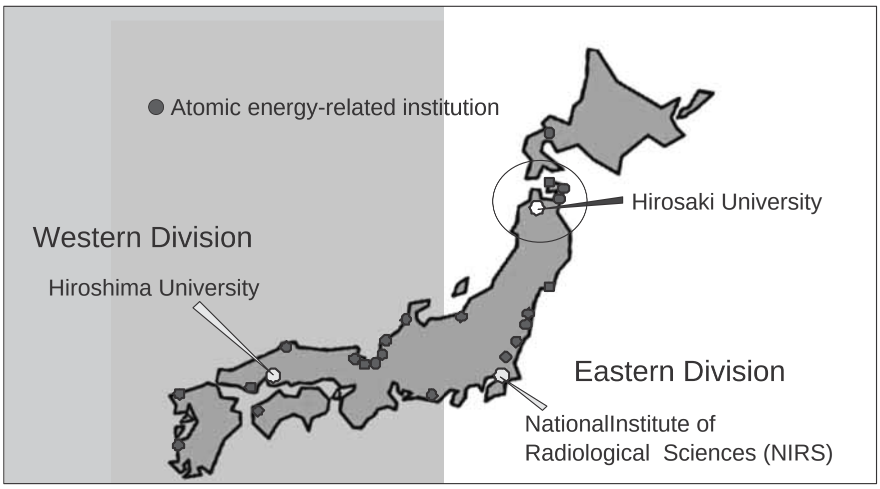

Fig1. The radiation emergency system in Japan

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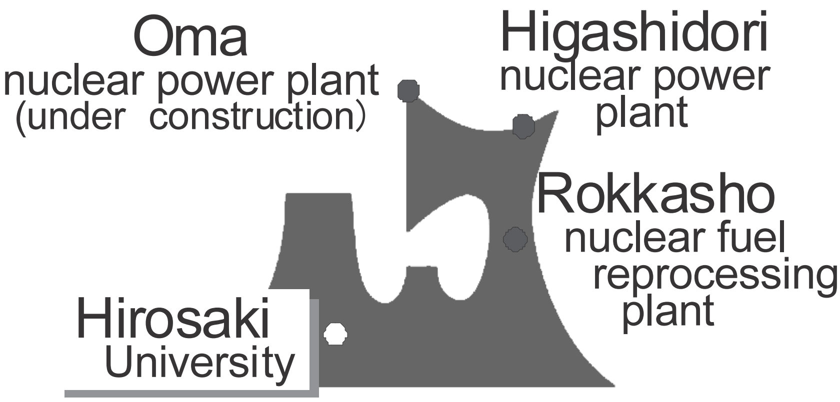

Fig2. Nuclear facilities in Aomori

The progress to date of the project

At the start of the project, clarification of the project goals has been discussed, and development of organized activity was aimed. As a concrete action, accumulation and summarization of knowledge, technology and information were conducted through a training and visit in the domestic and overseas related organization. Consequently, basic philosophy and the features of human resources were developed, and then the education curriculum was systematized. Additionally, research activities in the field of health care sciences were started systematically.

Basic educational philosophy and the features of human resources

Education program was consisted from three dimensions, such as the undergraduate, postgraduate and continuous education. The features of human resources which should be developed are as follows:

- In undergraduate education, they have basic knowledge in radiation emergency medicine as well as specialized knowledge and technology in each field.
- In Master's course, they have expertise in radiation emergency medicine, and they are capable of problem-solving under their leadership in an emergency such as a massive radiation disaster. Additionally, they are qualified to promote education and research in radiation emergency medicine. In continuous education, they are able to respond to possible radiation emergency medicine with their knowledge and skill according to their educational level.

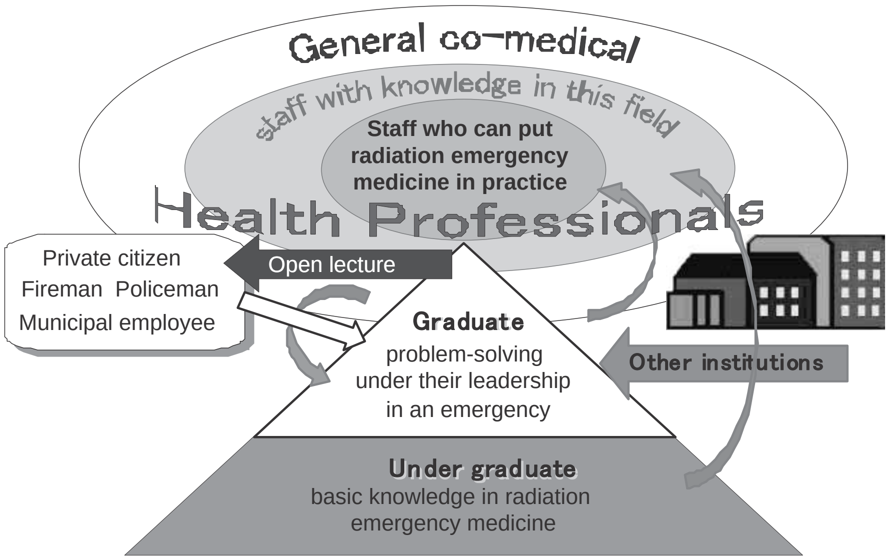

Fig3. Conceptual diagram of the basic educational philosophy

An accomplishment of the project to date

The basis of the new education in radiation emergency medicine for the health professionals was built. The future of human resources which should be developed was designed and the curriculum was systematized. The education in undergraduate and graduate courses was commenced, and first in-service training program was conducted.

Academic research on radiation emergency medicine was commenced in the field of health sciences. Furthermore, international symposium is organized continuously.

The challenge for the next step

Finally, the challenge for the next step is as follows:

- Working in close contact with the Institute of Education and Research in Radiation Medicine.
- Enhancing the education in undergraduate and postgraduate courses, and making the program of in-service training satisfactory.
- Promoting the academic research on radiation emergency medicine in the field of health sciences.
- Making public the accomplishments of the project in domestic and overseas.
- Enhancing the mission of this project in Hirosaki University.

Radiation Emergency Medicine education program at Hirosaki University

Toshiya Nakamura*, Education Group

Department of Biomedical Sciences,
Division of Medical Life Sciences,
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Hirosaki, Japan

Abstract. The Radiation Emergency Medicine Education program at Hirosaki University just started in April 2010. Our program includes three levels of education as described below. **(1) Education for Undergraduates** This program is aimed at undergraduate students to provide them with fundamental knowledge about radiation emergency medicine through "Introduction to Basic Radiation" and "Medical Risk Management". The first provides basic knowledge related to radiation protection and an outline of radiation emergency medicine, while the second provides further understanding of radiation emergency medicine and crisis-management involving cooperation among paramedical personnel. **(2) Education for Graduates** The "Radiation Emergency Medicine Course" was started as a Master's Course in our Graduate School of Health Sciences. Its aim is to prepare paramedical personnel to have advanced expertise and skills related to radiation emergency medicine, who can take the lead in emergency situations, and who can further promote education and research in radiation emergency medicine. In addition to each specialized subject, the students finish four required subjects and two optional subjects (Table I). **(3) Education for Paramedical Personnel** This is education for currently working paramedical personnel such as nurses and radiological technologists. Through this program, the paramedical personnel acquire the knowledge necessary for radiation emergency medicine and are trained to be able to deal appropriately with radiation.

Key Words: radiation emergency medicine, education, paramedical personnel

Introduction

For unusual radiation exposure including some accidents in nuclear plant or medical facilities, it is necessary to foster paramedical personnel who can correspond to the radiation emergency medicine. In 2008, Hirosaki University Graduate School of Health Sciences started to prepare the education program for our students to deal with radiation emergency medicine. It was not easy way for us because all of our faculty staffs were beginners in this field. But we could start our education of radiation emergency medicine in April, 2010.

Our program is made from 3 parts as following; Education for Undergraduate students, education for graduate students, and education for paramedical

Education of Undegraduates

As shown in Table I, there are five departments in Hirosaki University School of Health Sciences. Our mission is to foster paramedical personnel such as nurse, radiological technologist, medical technologist, physical therapist, and occupational therapist. All the students will have to pass their national examination at the end of their senior grade, so their curriculums are very tight by attending a number of classes, which have been designated by the Ministry of Education or Ministry of Health. Therefore, there was almost no room to put into some subjects related to Radiation Emergency Medicine in the schedule. This is still a difficult problem.

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Table I. Outline of Hirosaki University School of Health Sciences

Departments	Number of Students per Grade
Nursing	80
Radiological Technology	40
Medical Technology	40
Physical Therapy	20
Occupational Therapy	20

After all, we managed to have 2 subjects (Table II). These are "Introduction to Basic Radiation" in Liberal Arts education, and "Medical Risk Management" in faculty education. These classes are held at spring semester in Freshman and Junior grade, respectively. The objectives in "Introduction of Basic Radiation" are to have basic knowledge related to radiation protection, and to understand an outline of radiation emergency medicine. The contents of this course are;

1. Common sources of exposure to radiation
2. Ionizing radiation and interaction
3. Measurement
4. External and internal radiation hazards
5. Risks of radiation
6. Nuclear Plant and Nuclear fuel cycle plant
7. Overview of Radiation Emergency Medicine

As to the "Medical Risk Management", a class of "Risk Management" is currently opened for the students of all major, and we arranged this class by addition of the content for Radiation Emergency Medicine. The objective of this class is to understand crisis-management involving cooperation among paramedical personnel. The students are expected to understand the system of radiation emergency medicine from the standpoint of each profession.

Table II. REM-related subjects for undergraduate students.

Subjects	Grade, semester
< Liberal Arts Education > **Introduction to Basic Radiation**	1st Grade, Spring semester
< Faculty Education > **Medical Risk Management**	3rd Grade, Spring semester

Education for Graduates

"Radiation Emergency Medicine (REM) course" were established in Master's degree course (2-year course). The objectives of this course are 1) To have advanced expertise and skills related to radiation emergency medicine, 2) To be able to take the lead in emergency situation, and 3) To promote education and research in radiation emergency medicine.

After the graduate students go through the REM course, they can receive "Certification of REM Profession" which is authorized by Hirosaki University. The requirement for "Certification of REM Profession" was shown in Table III. The graduate students have to take; 1) Common Subjects for more than eight credits, including six credits related to Radiation Emergency Medicine, 2) Research Subjects for fourteen credits, all of them should be related to Radiation. 3) Optional Subjects for more than eight credits, including at least four credits related to Radiation Emergency Medicine.

The list of subjects was shown in Table III. For common subjects, the graduate students in Radiation Emergency Medicine course are required to take at least three REM related subjects, "Introduction to Radiation Protection", "Introduction to Radiation Emergency Medicine", and its "Seminar". In addition, they have to take "Research Seminar in Health

Table III. Requirement for Certification for REM Profession

Common subjects --- ≧8 credits
REM related --- 3 subjects (6 credits) Health Science related--- ≧1 subject (≧2 credits)
Research subjects --- 14 credits
Seminar --- 2 credits Advanced Seminar --- 2 credits Thesis --- 10 credits
Optional subjects --- ≧8 credits
REM related ---≧2 subjects (≧4 credits) Health Science related---≧2 subject (≧4 credits)

Sciences” in Health Science related subjects. These four subjects are compulsory. Optional Subjects were also listed in Table III. From “Nursing for Radiation Emergency Medicine” to “Rehabilitation Science & Radiation Emergency Medicine”, total twelve subjects are opened and the students have to take at least two subjects out of twelve.

An example of subject selection for the students was shown in Table V. Four “Common” subjects were shown, corresponding to eight credits. Research

Table IV. List of common and optional subjects of REM course in Master’s degree course.

Common subjects	**Credits** 1st grade	2nd grade
< REM related >		
Introduction to Radiation Protection	2	
Introduction to REM	2	
REM, Seminar	2	
< Health Science related >		
Medical Management	2	
International Health and Medicine	2	
Seminar of Cooperation in Health Sciences	2	
Research Seminar in Health Sciences	2	
Optional subjects (REM related)		
Nursing for REM	2	
Topics in Radiomedical Sciences	2	
Topics in Radiation Therapy Technology	2	
Topics in Radiation Biology	2	
Radiation Safety Control, Special Lecture	2	
Clinical Examination for REM	2	
Human Cytogenetics	2	
Chromosome analysis, Seminar	2	
Bioassay for REM	2	
Clinical Instrumental Analysis	2	
Clinical Instrument Analysis - Practice	2	
Rehabilitation Science & REM	2	

Table V. Example of subject selection in REM course

Subjects	**Credits**	**Total credits**
< Common subjects >		
Introduction to Radiation Protection	2	
Introduction to REM	2	8
REM, Seminar	2	
Reaserch Seminar in Health Sciences	2	
< Research subjects >		
Advanced Seminar for Cell Biology	2	
Cellular Biochemistry and Molecular Biology, Seminar	2	14
Cellular Biochemistry and Molecular Biology, Special Research	10	
<Optional subjects >		
Molecular Biochemistry	2	
Cell Biology	2	8
Human Cytogenetics	2	
Chromosome analysis, Seminar	2	
Total	30	

subjects are “Advanced Seminar for Cell Biology”, “Cellular Biochemistry and Molecular Biology, Seminar”, and “Special Research”. The contents of these subjects are depend on their supervisor’s specialty, and all of them should be related to Radiation and they are corresponding to fourteen credits. As to optional subjects, “Human Cytogenetics” and “Chromosome analysis, Seminar” are Radiation Emergency Medicine related subjects. “Molecular Biochemistry” and “Cell Biology” are Health Science related subjects. These are eight credits, and total is thirty credits. The students who finish these subjects can receive the “Certification of REM Profession”.

Education of paramedical personnel

This education program is opened for Nurses and Radiological Technologists who are currently working in medical facilities. The objectives of this program are to foster Nurses and Radiological Technologists who have; 1) the knowledge and the management ability necessary for Radiation Emergency Medicine, 2) an appropriate correspondence and cooperation each other during emergency, and 3) the ability to take care of the irradiated patients in medical care.

This year’s schedule for this program was already finished. For nurses, it is not sure that they have sufficient knowledge for basic radiation. Therefore, “Primary Course for Nurse” was held on August 28. As shown in Table VI, the participants learned basic knowledge about radiation by attending three classes entitled “Introduction to Radiation”, “Radiation Biology” and “Radiation Protection”. And then, “Basic Course for Nurse” was held in September 10-11. This was a two-day course. There were eight classes and one exercise, including 4 classes about Medical Radiation Exposure indicated by asterisk. (Table VI). “Basic Course for Radiological Technologist” was also held on September 10-11. Similar to the nurse course, there were eight classes and one exercise, but the contents were arranged for radiological technologist as shown in Table VI.

As to “Simulated Radiation Accident Exercise”, the participants in the course of both nurse and radiological technologist were joined and did it together. This exercise was made from “Table top exercise”, “Drill”, and “Review”. In “Table top exercise”, participants learned about the accident preliminary. In “Drill”, the participants played Doctors, Hot- and Semi-hot-area nurses and radiological technologists, and learned the handling and decontamination of contaminated victims. After the drill, participants and our staff reviewed their action. They discussed each other and tried to clarify their uncertain problem. They also confirm their skills and knowledge. Through this program, the participants learned the practical aspects of initial hospital management of irradiated and/or contaminated patients.

In order to perform this exercise, our staff had to practice for instruction training once a month, from April to August. They are devotedly contributing to this program. Let me express my appreciation to our staff.

Our education for Radiation Emergency Medicine just started. Without saying, it is not nearly enough. We would like to improve it to more substantial one, and contribute to fostering paramedical personnel for Radiation Emergency Medicine.

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Table VI. Contents of Paramedical Personnel Course

<table>
<tr><th>Course for Nurse</th><th rowspan="2">Course for Radiological Technologist</th></tr>
<tr><td>< Primary Course >
Introduction to Radiation
Introduction to Radiation Biology
Introduction to Radiation Protection</td></tr>
<tr><td>< Basic Course >
Introduction to Radiation Therapy*
Nursing in Nuclear Medicine*
REM and Nursing
Property and Protection of Radiation
Mental Health in Radiation Therapy*
Nursing in IVR*</td><td>< Basic Course >
Rule in REM
Cooperation among paramedical personnel
Basic Nursing Skill
Radiation Protection Treatment
Practice of Radiation Dose Calculation
Measurement of Radiation</td></tr>
<tr><td colspan="2">**REM System**
Mental Health in REM
Simulated Radiation Accident Exercise (Table top exercise, Drill, Review)</td></tr>
</table>

Acknowledgement

I greatly appreciate the devoted contribution of our staffs to the preparation and performing this education program. And I would like to express my special thanks to the member of the Education Group of Radiation Emergency Medicine Committee, Hirosaki University Graduate School of Health Sciences. The members are Saichi Wakayama, M.E., Tomoko Ichinohe, Ph.D., Chieko Itaki, Ph.D., Yoichiro Hosokawa, Ph.D., Yoshimitsu Otomo, Ph.D., Toshiko Tomisawa, M.S., and Manabu Nakano, M.S.

Development of human resources in health professionals, particularly in the field of Radiation Emergency Medicine

Kazuharu Nishizawa*, Sub-leader of the Planning Group(*)

Department of Radiological life Sciences, Division of Medical Life Sciences, Hirosaki University Graduate School of Health Sciences, Japan

Abstract. The purpose of the activity of the planning department is to plan staff education and training in radiation emergency medicine. These are divided into the following four categories and are conducted on an ongoing basis. **Training in and outside Japan:** In Japan, we participate in the training course on radiation emergency medicine of the National Institute of Radiological Sciences (NIRS), attend lectures on radiation emergency medicine sponsored by Aomori Prefecture, monitor the nuclear power emergency drills, and participate in nuclear power emergency drills sponsored by the Nuclear Safety Technology Center (NUSTEC). In 2009, we participated in a training workshop for PTSD (post-traumatic stress disorder) measures sponsored by the Japanese Association of Psychiatric Hospitals. Outside Japan, we participate in lectures held at the Radiation Emergency Association Center/Training Site (REAC/TS) of the US ORISE. In 2010, we conducted an inspection of and training at the French Hôpital d'instruction des armées (HIA) and Defense Radiation Protection Service (SPRA). **Training report meeting:** A report meeting for the above lectures and trainings are held to promote the sharing of all the staff's knowledge. This serves as preliminary education for untrained staff. **Lectures and seminars:** Specialists and persons with experience in radiation emergency medicine are invited as lecturers to hold lectures and seminars. Leaders in radiation medicine are invited from outside Japan and an international symposium is held once a year. The contents of the lectures are published on the internet and provided to the mass media to publicize information on radiation medicine to local communities and within and outside Japan. **Preparation of training reports:** Training reports are collated and content on the cultivation and utilization of human personnel will be summarized to be fed back into the education program. These will be basic materials to enhance staff training.

Keywords: staff education, staff training, seminars

Introduction

Two major problems were evident at the start of this project. Although the senior staff of radiological life sciences departments had a thorough understanding of acute radiation emergency medicine, none of the staff had practical experience and very few were sufficiently educated about basic radiology, radiobiology, radiation physics and radiochemistry.

Based on the current status, the planning group decided to educate the staff about

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(*)Planning Group: Yoshiko Nishizawa (Leader), Kohji Sumigawa, Ruriko Kidachi, Yuka Noto, Minoru Osanai, Takashi Ishikawa, Shoji Chiba, Chiaki Kitamiya, Hirokazu Narita radiation and radiation exposure and to implement staff training in radiation emergency medicine.

The following annual action plans were designed to achieve this goal within five years (Table).

Table Annual plan and schedule today

1. Staff training in and outside Japan
2. Training report meeting
3. Lectures and seminars
4. Preparation of training reports
5. The international symposium

Staff training inside and outside Japan

1. Staff training in Japan

1.1 Staff participated in radiation emergency medicine courses between 2007 and 2011 at the National Institute of Radiological Sciences (NIRS), which is the national center of radiation emergency medical preparedness in Japan. The institute provides direct or consultative services to local governments and hospitals in the event of incidents involving radiation, provides equipment and facilitates the establishment of networks of staff specializing in radiation exposure, contamination, dose assessment and radiation protection, and assists in the preparation of relevant documents and guidelines. NIRS also provides annual seminars about radiation emergency medicine aimed at health professionals. The purpose is to be able to respond to scenes of accidental radioactive contamination or exposure and to help staff to acquire the knowledge and skills required to support victims of such accidents. Eighty-two (85%) employees at this department have participated in these seminars since 2008 and 10 of them have also participated in the NIRS Radiology Seminar for Nurses. These training courses are critical because they are effective and valuable for this project. (Figs. 1 - 4)

Fig.1

Fig.2

Fig.3

Fig.4

1.2 Attendance at lectures on radiation emergency medicine sponsored by Aomori Prefecture (11 participants).
1.3 Monitoring nuclear power emergency drills, and participating in nuclear power emergency drills sponsored by the Nuclear Safety Technology Center (NUSTEC) (21 participants; Figs. 5 - 7).
1.4 Visits to Japan Nuclear Fuel Ltd. (JNFL) in Rokkasho-Mura and the Higashidori Nuclear Power Station in Higashidori-Mura (81 participants; Figs. 8 and 9)
1.5 Attendance at other meetings or societies related to radiation emergency medicine, such as meetings of the Japanese Association for Medical Management of Radiation Accidents and of the Research for Medical Management of Lymphatic Edema (46 participants; Fig. 10)
1.6 Attendance at opening lectures concerned with radiation emergency medicine such as “PTSD management after radiation accidents” and “Nursing radiation injuries or acute radiation syndrome” (Fig. 11).


Fig.5


Fig.6


Fig.7


Fig.8


Fig.9


Fig.10


Fig.11

2. Staff training outside Japan

2.1 Participation in accredited continuing education courses in radiation emergency medicine provided by The Radiation Emergency Assistance Center/Training Site (REAC/TS) at the Oak Ridge Institute for Science and Education (ORISE; Oak Ridge, TN, USA). Physicians, their assistants, nurses, emergency medical technicians, health physicists and first responders benefit from the lectures, discussions and hands-on exercises as they learn how to medically manage an incident involving radiation. Ten staff members participated in the Radiation Emergency Medicine Courses presented from October 21-24, 2008, August 18 - 21, 2009 and September 14 - 17, 2010 and five participated in Health Physics in Radiation Emergencies courses presented February 8-15, 2009 and 2010 (Figs.12 and 13).

2.2 Visit to the Hôspital d'Instruction des Armées (HIA) Percy and Defense Radiation Protection Service (SPRA; Paris, France), which is a military hospital with a particularly well-equipped department for the treatment of burn victims and of radioactively contaminated patients. (5 participants; March 22 - 28, 2010; Figs.14 and15)

Future plans

The present program must continue to improve staff capacity. However, participation requires considerable effort and imposes a burden on official or private time that is independent of their original occupation. In addition, their efforts and outcomes must be evaluated and a system to achieve this needs to be established. The ICRP Publication 103 (2007) states that, "They maintain the Commission's three fundamental principles of radiological protection, namely justification, optimization and the application of dose limits..." Hence, evaluation and review of outcomes should focus on ***justification*** and ***optimization*** if this project is to continue.

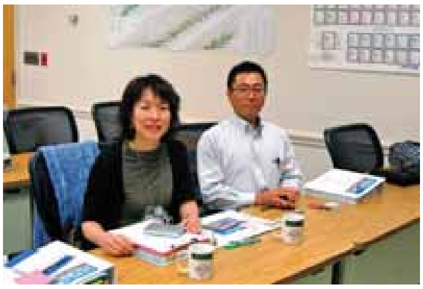

Fig.12

Fig.13

Fig.14

Fig.15

Domestic cooperative activities of the regional collaboration group

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Abstract. We report the main activities of the Regional Collaboration Group. Our Group's missions are development of a close relationship with other institutes and the local government office, information gathering, and publicity.
We first attended study tours at the Japan Nuclear Fuel Limited (JNFL) Higashidori Nuclear power station and at the National Institute of Radiological Sciences (NIRS). Through these study tours, we obtained basic knowledge of radiation and radiation emergency medicine. We also visited other Prefectural Governments, such as Ibaraki Prefecture, Fukui Prefecture, and Niigata Prefecture. In addition, we also visited Tokai-mura, and Rokkasho-mura. Through these visits, we learned much about the regional network of radiation emergency medicine, training systems for personnel in radiation emergency medicine and management, and problems encountered in past radiation emergency accidents.
Publicity includes a project overview and reports of results on our website and publication of brochures. With the support of many other staff, especially the secretary general, the website of the Project to train Radiation Emergency Medicine staff is now available (http://www.hs.hirosaki-u.ac.jp/~hibaku/). Though the website has gradually expanded, we are planning to enrich the content of our website. The latest edition of our leaflet has just been published recently, and we are planning to distribute it to the general public.

Key Words: Domestic Cooperative Activities , Regional Collaboration Group,

Preface

The structure of the project to train radiation emergency medicine personnel at Hirosaki University Graduate School of Health Sciences was reorganized in 2009, and the Regional Collaboration Group was formed, centered on the former Information Collection Group. The main activities of our group are information gathering and publicity. Many of our group's activities are carried out in close cooperation with other groups (Panning Group, Education Group, and Research Group).

The missions of our group are as follows:

・development of a close relationship with other institutes, local government office, etc.
・information gathering
・publicity

In this paper, the activities of the Regional Collaboration Group are presented.

Close Relationship with other Institutes

To train radiation emergency medicine personnel and develop a system for such training at our university, our university has concluded agreements with Japan Nuclear Fuel Limited (JNFL) and the National Institute of Radiological Sciences (NIRS) (Fig.1).

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Members: Yoko Saito, Kumiko Saito, Takao Osanai, Hiroyuki Nozaka, Terumi Kogawa, Kiyotada Washiya

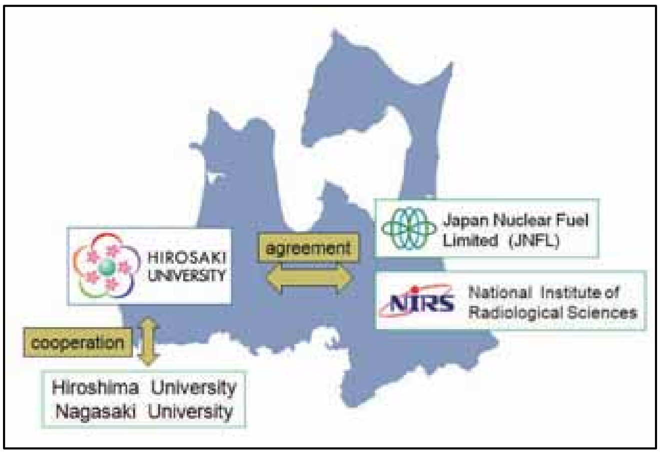

Fig.1 Relationships with other Institutes

We now have three companies that are cooperating with us in Radiation Emergency Medicine Education at Hirosaki University:

・JNFL
・Tohoku Electric Power Co.
・Institute for Environment Sciences (IES)

Our group has maintained a close relationship with these institutes in cooperation with other groups.

Information Gathering

The group's information gathering activities include gathering various types of information associated with radiation emergency medicine in cooperation with various organizations outside the university. To train radiation emergency medicine personnel and develop a system for such training at our university, our university has concluded agreements with JNFL and the NIRS. Therefore, we first attended study tours at JNFL Higashidori Nuclear power station and at the NIRS. Through these study tours, we developed a close relationship with these institutes and obtained basic knowledge about radiation and radiation emergency medicine. We also received valuable and helpful advice on the training system for radiation emergency medicine personnel.

We are also working together with Hiroshima University and Nagasaki University, and we visited these universities and gathered information on their personnel training systems for radiation medicine and radiation medicine organization systems.

We also visited other Prefectural Governments such as Ibaraki Prefecture, Fukui Prefecture, and Niigata Prefecture. In addition, we visited Tokai-mura and Rokkasho-mura. Through these visits, we learned much about regional networks of radiation emergency medicine, training systems for personnel in radiation emergency medicine and management, and problems encountered in past radiation emergency accidents. In addition to data collection, we received valuable advice and many suggestions for training of radiation emergency medicine personnel.

We also attend, as observers, meetings of the Aomori Prefecture Special Committee on Radiation Emergency Medicine Measures. We receive information about the present status and problems in the radiation emergency medicine network system in Aomori prefecture

We also obtained information about radiation emergency accidents and accidents in nuclear power plants, other nuclear plants, and other X-ray institutes from the records of regular meetings of the Nuclear Safety Commission (NSC) through the website
http://www.nsc.go.jp/anzen/shidai/index.htm.

Publicity

Our publicity activities include a project overview, and reports of results on our website and publication of brochures.

With the support of many other staff, especially the secretary general, the website (Fig.2) of the Project to train Radiation Emergency Medicine personnel is now available
(http://www.hs.hirosaki-u.ac.jp/~hibaku/).

Though the website has expanded gradually, we are planning to enrich the content of our website

Fig.2. The Website of the Project to train Radiation Emergency Medicine Personnel

The First and Second editions of the leaflet have been published. The latest (Second) edition has just recently been published (Fig. 3). We are planning to distribute our leaflets to the general public.

In the Future

At the end of this paper, our group's future plan should be described. First, we are planning to digitize the data we have collected to create PDF files and create a database of this information. This will help us release this information to the public.

An English version of our website is also planned.

Fig.3. The front page of the second edition of the leaflet.

Necessity of emergency medical treatment team for radiation injuries

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Background: Serious nuclear accident occurred during Uranium conversion process on September 30, 1999. This resulted in seriously irradiated three employees at the plant. We report the clinical course of these employees and evaluate the role of the National Institute of Radiological Sciences (NIRS) and the Emergency Medical Treatment Network for Radiation Injuries.

Clinical course: The three patients received initial treatment at Mito National Hospital and were then immediately transferred to the NIRS hospital. Based on the results for peripheral lymphocyte reduction rate and blood sodium-24 levels, the estimated doses received by the three employees were 17-22 Gy, 8-10 Gy, and 1.8-2.5 Gy, respectively.

The most serious patient, transferred to the University of Tokyo Hospital on Day 3 to receive HLA type matched peripheral stem cell transplantation. Thereafter the bone marrow function recovered after transplantation, However, skin and GI disorders worsened, resulting in death three months after exposure.

The next serious patient also transferred to Medical research institute of the University of Tokyo Hospital on Day 5 for umbilical cord blood stem cell transplantation. Since skin damage of hands, face, and lower extremities had worsened, cadaveric skin allografts were implanted at Dec.20,1999 and cultured allograft skin were implanted at Dec.28,1999. Under careful skin treatment and rehabilitation, the employee has been improving gradually. The emergency medical treatment team provided long-term support in the hematology, intensive care and burn treatment.

Another patient received treatment for bone marrow suppression in a clean room of NIRS hospital. After the recovery of the bone marrow function was confirmed, he was transferred to a general ward and was later discharged.

Discussion: The Emergency Medical Treatment Network for Radiation Injuries functioned well, and provides advanced treatment to the three employees. Treatment of severe radiation injuries requires both innovative medical techniques and management with facilities such as intensive care units, burn units, and bio-clean rooms. For this reason, a treatment group should include specialists in emergency medicine, intensive care, bone marrow transplantation, burn surgeon, and radiologist. To provide appropriate care for radiation victims, a cooperation system among these specialists as well as efficient advanced treatment facilities should be prepared

Nursing patients of the JCO criticality accident

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The worst radiation accident in Japan occurred 10 years ago. This was the JCO criticality accident. Radiation accident requiring medical care is rare. So I think that the lessons learned from the experiences of this accident should be shared. As a nurse involved in patient care at that time, today I would like to introduce my experiences.

Outline of the JCO accident

A criticality accident occurred at a uranium processing plant in Tokaimura, Ibaraki prefecture, at 10:35 in the morning on September 30, 1999. Three workers were exposed to high doses of radiation. The first report arrived at NIRS from the Fire Department at 11:20 a.m. At this time, the priority was emergency treatment of the patients, and they were transported to National Mito Hospital, a secondary radiation medicine facility. These three patients received emergency treatment at Mito Hospital. However, high-dose exposure symptoms appeared, and radiation was detected on the body surface of the patients. Therefore, it was decided to transport them to NIRS, a tertiary radiation medicine facility. About five hours after the accident occurred, they were transported by helicopter a distance of about 120 km to the emergency radiation medicine department of NIRS. The radiation detected on the surface of the body was from radio-activation of stable elements within the body as a result of neutron exposure.

From now I will call the three exposed employees Mr. A, Mr. B, and Mr. C. Immediately after the accident, Mr. A lost consciousness for 20 seconds and showed stiffness of the entire body. He also vomited and, within one hour, he had diarrhea. Mr. B also had nausea and vomiting within one hour. Mr. C did not show any obvious symptoms, but after four hours, only nausea was observed.

The estimated exposure was 16-20 Gy to Mr. A, who was closest to the precipitation tank when criticality occurred, 6-10 Gy to Mr. B, and 1-4.5 Gy to Mr. C.

Radiation emergency medical preparedness in Japan

Here I'll explain the system for the radiation emergency medical preparedness in Japan. In Japan, treatment for radiation exposure is performed at 3 levels: primary level in hospitals near nuclear facilities: secondary level in local general hospitals, and tertiary level by more equipped and advanced hospitals. Hospitals at the primary level provide first-aid treatment, primary assessment of contamination with radionuclides, and removal of contamination on the body. Therefore, these hospitals have to be equipped with radiation detectors such as survey meters and the minimum requirement for decontamination. Secondary-level hospitals provide medical and radiological triage, decontamination, and treatment of local radiation injuries and whole body exposure, and also start treatment for internal contamination. Thus, most medical facilities at the secondary level are general hospitals. In the JCO accident, the National Mito Hospital served as the secondary radiation medicine facility. Tertiary hospitals receive patients heavily exposed to radiation and/or contaminated and to provide diagnostic and prognostic assessments of radiation-induced injuries and biological and radiological dose estimation. In Japan, the National Institute of Radiological Sciences and Hiroshima University are tertiary radiation medicine facilities. They accept patients exposed to severe high doses of radiation and those exposed to high levels of internal contamination, and they provide specialized decontamination and medical care.

Acceptance and care of patients

To prevent contamination, a plastic sheet was placed on the floor of the decontamination room, and a controlled area was established to prevent spread of contamination. Stretchers and beds were covered with polyethylene filter paper.

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Medical teams were formed to handle the patients. The medical teams had one doctor and two nurses for each patient. People who would enter the hot area and be directly involved in decontamination or medical care wore radiation protective suits and overshoes, and they were equipped with half face masks and plastic gloves over cotton gloves.

At this time, there was no accurate information about whether or not there was external or internal contamination, or the level of contamination. Therefore, basic preparations were needed to prevent the spread of contamination and avoid secondary exposure to medical personnel. Some people have said that the outfitting was excessive. However, we received the patients without accurate information. Therefore, these kinds of preparations were unavoidable for medical personnel.

After the patients arrived, a full body survey was done by the radiation protection expert. At the same time, the medical team confirmed the patient's consciousness level, checked vital signs, collected blood, and collected specimens from nasal smears. Mr. A and Mr. B showed prodromal symptoms of acute radiation syndrome. They were treated for vomiting and diarrhea, and excrement was stored for safe disposal. Mr. A had low blood pressure, and intravenous transfusion of physiological saline was begun. The clothes they were wearing and the linens they used were put in plastic bags and kept for safe disposal. Afterwards, the results of the survey demonstrated exposure to gamma radiation and neutron radiation, indicating the strong possibility that the accident was a criticality accident. Since emergency care and treatment for bone marrow suppression would now take priority, the patients were placed in reverse isolation at hospital of our institute.

At the same time, a meeting was held of the Medical Network Council for Radiation Emergency, with experts from our institute and other advanced medical institutions, and the treatment strategy for the three patients was decided. During transport from the radiation emergency medicine facility to the hospital, protective measures included putting up polyethylene filter paper in the corridors on the transport route. The floors and beds in the reverse isolation room were also protected, and dosimeters were set on the walls of the patient room and in the front chamber and halls.

Mr. A continued had frequent vomiting and diarrhea even after entering the reverse isolation room. He also had a headache that was thought perhaps to be from blood vessel dilation. To prevent the spread of contamination from excrement, the gargling basin, portable toilet, and plastic bucket were covered with plastic bags for use. Vomit, feces, and other excrement were checked each time for occult blood to confirm gastrointestinal bleeding. Oxygen administration was begun, a line for total parenteral nutrition (TPN) was placed, and fluid infusions were managed. Administration of antibiotics was begun to prevent infection. A central venous pressure (CVP) line was placed, and an electrocardiogram monitor was attached. Each hour, vital signs were checked, and CVP and oxygen concentration were measured. A urethral catheter was placed because of urinary retention. For laboratory tests, blood sampling and nasal and oral smears were conducted frequently. Bone marrow aspiration and bone marrow biopsy were also done. After a bed bath, towels, clothes, and used forceps were placed in a plastic bag and stored. Every morning, a radiation protection expert surveyed the stored items and then disposed of them. All procedures, tests, and physical care were done with sterile techniques to prevent infection. The patients at this time expressed dissatisfaction with the frequent tests and procedures and said things that worried their families. Performing procedures under aseptic control and prevention of the spread of contamination were a source of stress for both patients and medical personnel. Nearly the same procedures and nursing care were done for all three patients. Nurses outside reverse isolation room also played important roles. These roles included assisting the nurses working inside, contacting to families and making records. The mass media were also obtaining information from other patients, and there were people who felt anxious being near the radiation patients. We had to explain to these patients that there was no danger and ensure their understanding. Mr. A and Mr. B developed progressive bone marrow suppression and were put under stricter aseptic control. Mr. A was transferred to a hospital for stem cell transplantation from peripheral blood on the third day of hospitalization. Mr. B was transferred to a hospital for cord blood transplantation on the fifth day of hospitalization.

Mr. C was put under semi-aseptic control and continued in our hospital. On the fifth day of hospitalization, a nursing care plan care for Mr. C was made. There were two nursing problems: infection and anxiety. For infection, instructions were given for oral care, cleaning of the nasal cavity, and breathing exercises to prevent respiratory infection. The CVP line was regularly sterilized and exchanged, and body cleanliness was maintained with regular shampooing and foot baths. MRSA was detected from the skin, but an isodine medicated bath was effective. We also instructed that the genital and anal areas were to be disinfected every time the patient defecated. An isolator was set up in the patient's room, and the medical staff wore a sterilized gown to prevent infection in the room. Sterile sheets were used and changed every day. Since the patient was involved in the accident, he felt guilty strongly. Therefore, to prevent anxiety, mass media information from the outside was prohibited. His wife was a key person, and she stayed with him as much as time allowed. He was also encouraged to stay awake during the day to sleep well t night. He liked reading, and so books and maps were sterilized and brought into the room. Regular counseling was also conducted by a psychiatrist. Mr. C had no complications, such as serious infection or bleeding, and he left the hospital after about three months.

Nursing system

Next, I'll describe the nurses' work system. Following the manual for emergencies, the nurses changed from three working shifts to two working shifts. In addition, our hospital did not have a system that could accommodate serious patients, and the Medical Council for Radiation Emergency Network requested cooperation from the Ministry of Welfare, and a total of 56 nurses from three institutions were sent to our hospital for one week.

Key points in radiation emergency medicine –for Nurses-

A questionnaire survey was later conducted of nurses involved in nursing for these radiation patients. Issues seen from the results included the following. Information on the accident was not communicated to nurses, and it took some time to understand the entire accident. Nurses had to respond to various instructions from many doctors, resulting in confusion. When receiving many phones, nurses had to run around each time for confirmation. Work was exhausting both mentally and physically during continuous duty for 16 hours. It was not easy to work together with nurses from other facilities, and roles and responsibilities should be clarified.

1. Necessity of acquiring basic knowledge about radiation and emergency training
2. Communication of accurate information
3. Leadership with accurate judgments and ability to take action
4. Assignment of people responsible for dealing with the mass media
5. Establishment of a nursing system for radiation emergency
6. Mental support for patient, family, and medical personnel

Through this experience, we realized that, for nurses, basic knowledge and regular training is essential important for emergency settings. Mental support is also important for the patients, because they were victims and also people who caused the accident. I recently met Mr. C when he came in for a regular checkup. He said quietly, "Even though nuclear energy is necessary for our lives, accurate information is not communicated to the public. It almost seems people involved in nuclear energy are trying to hide it. This arouses negative feelings in the public." It seems that, even within Mr. C, major issues remain unresolved.

An experience of physical therapy for the victim of the JCO accident.

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The JCO criticality accident had occurred in 1999. Three workers, who had exposed high dose neutron at the nuclear fuel conversion test factory, had suffered fatal radiation injury that anyone had never experienced. They were treated with most advanced quality level of intensive care consisted by facilities of emergent radiation injury medical network and multidisciplinary medical team.

The author had been belonged that team as a physical therapist from the Burn Center of Kyorin University Hospital, and executed a victim's treatment. It was aimed to assist of his recovery from radiation skin injury (radiation burn) firstly. However, radiation injury had invaded genetic level of cell function, which meant the damage to the cell from radiation injury was markedly difference from common thermal injury. According to time course, we should develop the subjects of evaluation and treatment into support of intensive care, because that the victim had appeared multiple organs failure severely, but it was hard to predict these symptoms and prognoses.

The roles of a physical therapist were following;

1)Evaluation

(1) wound/graft conditions.
(2) musculoskeletal functions
(3) physical assessment of cardiovascular and pulmonary conditions.

2) Therapeutic Interventions

(1) wound dressing, compression and skin care
(2)ROM exercise and splinting
(3) strength training
(4) develop ADLs
(5) positioning
(6) chest physical therapy

In our challenge, a physical therapist should face on not only musculoskeletal disorders but also cardiovascular, pulmonary and immunologic problems to conquer unknown and incremental pathophysiologic appearances caused by high doze neutron and gamma ray radiation injury.

These interdisciplinary knowledge and treatment skills are necessary and essential stuff of the staff in emergent intensive care team that confronts unfortunately heavily irradiated patients.

Medical management of radio-contaminated or irradiated wounded: the mission of education of the French Defense radiation protection service

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Abstract: The French Defense radiation protection service (SPRA) is located on the site of the Percy military hospital which is well known for the treatment of radio-contaminated and irradiated wounded. Education in the framework of the medical management of such patients is one of the major missions of this service. First of all, the SPRA usually helps the Percy hospital to organize exercises with its Center for the treatment of radio-contaminated wounded (CTBRC) or with the surgical unit inside the hospital. The SPRA is involved in numerous military and civilian training courses coordinated by the French armed forces health service (Military School of Val-de-Grâce, Master CBRN, Universities of Medicine, Moroccan co-operation), especially to teach the principles of the medical response in case of a radiological accident (triage of absolute and relative emergencies, specific techniques and drugs, psychological aspects). The SPRA takes part in the teachings concerning the organization of the Ministry of Defense in case of a radiological event (e.g. with the School of the military applications of the atomic energy). During the exercises performed by the French Navy or Air Force (transportation of a nuclear weapon, accident on a ballistic missile submarine), it advises the headquarters and plays the role of arbitrator.

Key words: Education – Emergencies – Radiation protection – Radioactive contamination – Irradiation.

The French Defense radiation protection service (SPRA) is born in 1973 from the Research Center of the French armed forces health service. It is considered by the Ministry of Defense as the technical support of military units in the framework of radiation protection.

1. LOCATION AND MISSIONS OF THE SPRA

The SPRA is located on the site of the Percy military hospital area which is well known for the treatment of radio-contaminated and irradiated wounded. It runs with two main divisions (65 military and civilian employees): a medical division and a technical division. It is directly subordinated to the director of the French armed forces health service (SSA) and its major missions are described in a specific decree (2005):

- occupational Medicine, especially the medical and radiobiological supervision of people exposed to ionizing radiation;
- hygiene and safety (technical controls of installations);
- regulation;
- intervention in case of a radiological event;
- education (more than 1 000 hours per year).

The Percy military hospital area is specialized in the management of military or civilian emergencies (e.g. wounded from Afghanistan). It is situated in the city of Clamart, near a railway, in the South-West of Paris. It is also specialized in the medical management of radio-contaminated and irradiated wounded. In fact, the Percy military hospital area is made up of:

- an academic hospital with an heliport and units like an emergency unit, plastic surgery, hematology, physical therapy and rehabilitation medicine, and psychiatry;
- a burn care unit (CTB);
- a blood transfusion center (CTSA);
- a center for the treatment of radio-contaminated wounded (CTBRC);
- the SPRA which is directly involved in the management of radio-contaminated wounded (four specialists in radiation protection, radio-toxicology and dosimetry units, anthroporadiametry, mobile laboratories that could be deployed by road or by aircraft) and which could be considered as an administrative entrance for the management of irradiated wounded.

It's therefore a great opportunity for the SPRA to be located inside the Percy military hospital area and to run with these kinds of specialized units which are present on the same site.

2. RELATIONSHIP BETWEEN THE SPRA AND THE PERCY HOSPITAL

Education is one of the major missions of the SPRA. First of all, this mission concerns the Percy hospital not only in the framework of the medical management of radio-contaminated and irradiated wounded but also for the radiation protection of the workers and the patients, and the organization of the training course of the radiation safety officers (in fact for all the Ministry of Defense). For example, teachings are organized with the SPRA each year to welcome the new employees and to demystify the radioactivity. Several meetings are planned as well to speak about dosimetric incidents, controls of the installations,...

The Center for the treatment of radio-contaminated wounded (CTBRC) is the main subject of our teachings, especially for the emergency unit crew. We usually underline the aim of this specific facility: to transform a radio-contaminated wounded in a decontaminated and stable patient. The three zones of the CTBRC are described: the first one is the room of triage with a codified undressing of the patient; the second one is the way of absolute emergencies and the third one, the way of relative emergencies with standing or lying patients. The students have to understand the six golden rules about the management of such wounded:

1. medical emergency is always the top priority;
2. the target is to limit the spread of the external contamination (for example, using vinyl sheets to protect the patient or the stretchers...);
3. in any case, you should not have to transform an external contamination in internal contamination (careful decontamination with an efficient protection of the wounds, never using a hot water...);
4. treatment of internal contamination is administered as soon as possible, without waiting for any result of a medical analysis;
5. detection is an important phase of the process and can be performed only on a dry skin;
6. an irradiated patient does not irradiate.

The SPRA usually helps the Percy hospital to organize exercises with its CTBRC (**figure 1**) or with the surgical unit (**figure 2**) inside the hospital (e.g. haemostatic surgery). It has initiated for the French armed forces health service conventions with institutions like the French Atomic Energy Commission (CEA), EDF Group (Electricité De France) or the French Radiation Protection and Nuclear Safety Institute (IRSN) in order to supply the best medical care for an ionizing radiation victim. For example, during the last exercise, the SPRA was in charge of the medical scenario concerning wounded coming from a Belgian nuclear power plant and from the CEA.

Figure 1. Exercise in the CTBRC of the Percy military hospital.

Figure 2. Exercise in the surgical unit of the Percy military hospital (haemostatic surgery).

In real life, the SPRA has a good experience of the management of a radio-contaminated wounded and can be considered has an administrative entrance for the medical management of an irradiated victim. This experience is a good point for our teachings.

3. TEACHINGS COORDINATED BY THE FRENCH ARMED FORCES HEALTH SERVICE

The SPRA is involved in numerous military and civilian training courses coordinated by the French armed forces health service to teach the principles of the organization of the medical response in case of a radiological accident. These teachings are dedicated to the Military school of Val-de-Grâce (EVDG – Paris), civilian universities of Medicine (e.g. Emergency and Occupational Medicine diploma) or for the benefit of foreign students (e.g. Moroccan co-operation).

Our teachers have to focus on very important points:

- -the missions and the means of the French armed forces health service and the relationship with the civilian authorities;
- -the different zones which are established around the scene of the accident (or the terrorist attack) to identify the affected population, to protect and control the public and the members of the emergency services, to facilitate the operations of all crews and to guard the scene (controlled area or red zone – yellow zone);
- -the triage of absolute and relative emergencies and the way of involved victims (physically fit) which is not a medical way;
- -the main features of the medical management of a radio-contaminated or irradiated wounded (cf. communication of Professor Pierre Laroche), the specific techniques, drugs and analysis (whole body or thyroid counting, radio-toxicology, biodosimetry, electron paramagnetic resonance…) that could be used in this case and the importance of psychological aspects;

- -the management of primary contaminated decedents which is not a mission for the medical crews; body of deceased people may constitute a radiological hazard, so the contaminated corpses must be placed in a body bag using appropriate labelling and visible radiation signs and must be
- moved in a temporary morgue under judicial control.

Students have to realize that this organization is connected to special facilities (**figure 3**) like CTBRC, PABRC (Advanced post for radio-contaminated wounded) or CTDS (Broad decontamination post for the way of involved victims). The CTBRC can be compared to a PABRC with a surgical unit (way of absolute emergencies): they are inspected regularly by the SPRA. All these military facilities associated to civilian facilities make a kind of net in our country (**figure 4**).

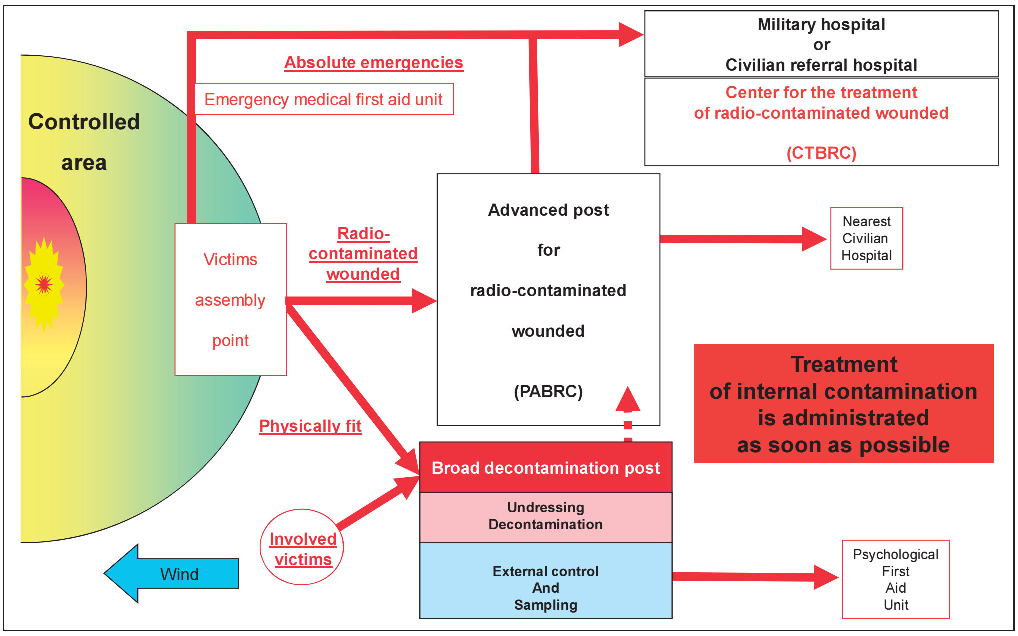

Figure 3. Medical organization in case of a radiological accident.

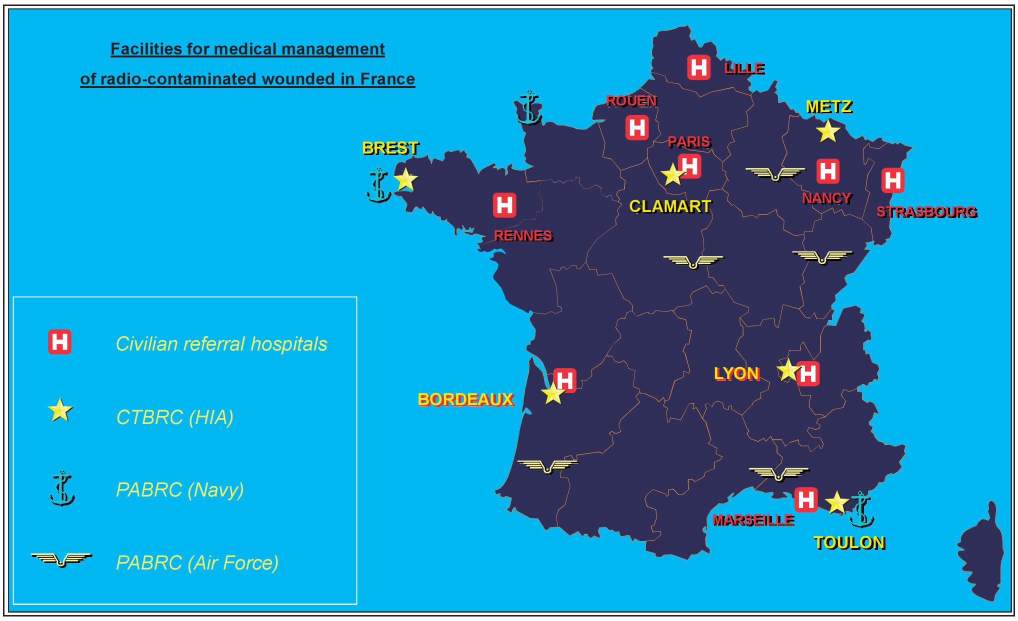

Figure 4. Net of CTBRC, PABRC and civilian referral hospitals in France.

The best example to illustrate the mission of education of the SPRA in the framework of the medical management of radio-contaminated and irradiated wounded is given by the new Master CBRN organized since 2009 by the Military school of Val-de-Grâce, the University of Medicine of Paris 6 and the French Atomic Energy Commission (CEA). This Master is opened to military and civilian medical practitioners, pharmacists, veterinarians or nurses. The students have to pass an exam after three hundred hours of theoretical lectures and must present a report after a three months practical training course. The SPRA is involved directly in this Master for the Nuclear and Radiological module coordinated by the Professor Laroche. The teaching of this theoretical module (60 hours) is based on basic knowledge of radioactivity and detection; the biological effects of ionizing radiation; the physical, biological and clinical dosimetry; the medical management and the treatment of radio-contaminated and irradiated wounded and the national emergency plans. The students have the possibility as well to validate only one theoretical module (Chemical, Biological or Nuclear and Radiological module) and two optional modules for a University diploma (120 hours).

4. TEACHINGS CONCERNING THE ORGANIZATION OF THE MINISTRY OF DEFENSE IN CASE OF A RADIOLOGICAL EVENT

The SPRA takes part in the teachings concerning the organization of the Ministry of Defense in case of a radiological event for the benefit of:

- the Joint School of the military applications of the atomic energy (Nuclear and safety superior course – EAMEA);
- the French Navy (medical officers and nurses serving on a ballistic missile submarine);
- the French Air Force (nuclear bases).

A joint order describes this organization in the framework of a peaceful time or a terrorist attack. In this case, the goal is to limit the consequences of the dispersal of the radioactive wastes on population and environment, to control the situation as fast as possible and to recover the safety of the nuclear facility. The activation of this plan is under the responsibility of the French Ministry of Defense and concerns systematically national and local levels. An efficient interface with the Prefect and the civilian authorities is very important. The communication with the public is organized at the local level between the journalists and the commander of the involved military unit associated to the Prefect, in connection with the national military and civilian authorities.

Our teachings underline the mission of the French armed forces health service and the SPRA during the three classical phases of a nuclear or radiological accident. During the initial response (phase I: about six hours), the SPRA (which is not an emergency medical first aid unit) is alerted by messages and fax from the Joint staff crisis center (CPCO) and gives the alarm to the Joint Staff of the French armed forces health service and the nearest military hospital with a CTBRC. During the analysis phase (phase II: about 24-48 hours), the SPRA medical advisor supports the Crisis management national center (national level) and an expert team (one medical officer specialized in radiation protection and one technician) joins the Local control and command post (local level). The SPRA is on call 24 hours a day, seven days a week, and can send on the spot an analysis team (mobile laboratories with one pharmacist specialized in radiation protection, three technicians and one secretary). These mobile laboratories (one truck for radiochemical analysis and two trucks for spectrometric analysis) can be deployed, by road or by aircraft (**figures 5 and 6**), in France or overseas, if requested by military or civilian authorities. During the remediation phase (phase III: weeks or months), the mobile laboratories run for occupational Medicine reasons.

Figure 5. Presentation of the mobile laboratories of the SPRA.

Figure 6. Mobile laboratory of the SPRA deployed by aircraft.

During the exercises performed by the French Navy or Air Force (transportation of a nuclear weapon, accident on a nuclear air base or a ballistic missile submarine...), the SPRA advises the headquarters and supports local health services. Another joint order describes the organization of the four kinds of exercises:

- level 1 (elementary exercise) to test transmissions and basic training;
- level 2 (superior exercise) to test the inner emergency plan (PUI);
- level 3 for nuclear safety;
- level 4 for civilian security to test the particular plan of intervention (PPI) of the Prefect.

The SPRA is in charge of the preparation of the medical scenario of the level 3 and 4 (three national exercises per year) and plays the role of arbitrator during the action. The participants are debriefed at the end of the exercise and the annual report concerning all the exercises, made by the Joint chief of staff for the nuclear forces (EMA/FN), is always a very interesting feedback for our teachings.

The SPRA is located on the site of the Percy military hospital area which has a good experience in the medical management of radio-contaminated and irradiated wounded. Education in this specialized field is one of the major missions of the SPRA. It is involved in numerous military and civilian training courses or exercises and especially in the new Master CBRN. Nevertheless, there is no choice but to accept that there is usually a lack of information and training on the management of such victims with the Health professionals. Nowadays, in the terrorist context that we know and with the dismantling of a lot of nuclear facilities, this mission of education is a top priority.

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Medical management of radio-contaminated or irradiated wounded: contrasts and paradoxes

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Abstract: There is an irrational perception of the exposure to ionizing radiation as much by the general population that by the Health professionals. This perception is the result of a lack of information and training on the management of radio-contaminated and irradiated wounded and especially about the real risks related to such exposure for all the medical crew. Objective knowledge about the effects of ionizing radiation, based on physical, biological and epidemiological studies, allows us to propose simple rules to take in charge these kinds of victims. The aim of our teaching is precisely to provide practical information to ensure maximum safety for the management of a radio-contaminated or irradiated wounded. During the training courses performed by the French Defense radiation protection service (SPRA), our teachers have to emphasize four subjects (the radiological risks for the victim, the priority for the treatment, the type of medical management and the risks for the medical crew) highlighting the contrast between the only two modes of exposure to ionizing radiation: contamination and irradiation.

Key words: Education – Emergencies – Radiation protection – Radioactive contamination – Irradiation.

Any contact with a radioactive source involves an exposure to ionizing radiation. These physical phenomena are the cause of a wrong perception as much by the general population and the journalists that by the Health professionals. This perception is the result of a lack of information and training on the management of radio-contaminated and irradiated wounded and especially about the real risks related to such exposure for all the medical crew. This information gap is often expressed as a conclusive statement of a lack of knowledge on the subject.

Objective knowledge about the effects of ionizing radiation, based on physical, biological and

epidemiological studies, allows us to propose simple rules to take in charge these kinds of victims.
The aim of our teaching is precisely to provide practical information to ensure maximum safety for the management of a radio-contaminated or irradiated wounded. During the training courses performed by the SPRA, our teachers have to emphasize four subjects:

- the radiological risks for the victim;
- the priority for the treatment;
- the type of medical management;
- the risks for the medical crew;

highlighting the contrast between the only two modes of exposure to ionizing radiation: contamination and irradiation.

5. RADIOLOGICAL RISKS FOR THE VICTIM

First of all, students have to know the difference between the two types of effects due to ionizing radiation. Deterministic effects appear above a threshold dose. Their severity depends on the dose and they are a direct result of cell death in the irradiated tissue. On the contrary, stochastic effects are not related to an individual threshold. Inside an exposed population, their frequency increases with the dose and the radio-induced cancer are indistinguishable from a spontaneous disease. Another important difference between these two kinds of effects is the time of occurrence. Deterministic effects can appear early after exposure, a few days to weeks, depending on the dose and the exposed tissue. Stochastic effects are late, several years after exposure for leukemia and several dozen years for sarcomas.

CONTAMINATION AND LONG-TERM EFFECTS

As we repeat to our students, deterministic effects will occur only beyond a certain amount of exposure (threshold). In a practical way, this threshold depends on the sensitivity of tissues and is never less important than 1 Gray.
An example of internal contamination may be provided by the use of radio-iodine for the treatment of diseases of the thyroid gland, responsible for hyperthyroidism. In this case, it is necessary to use a dose of 90 Gray in the thyroid tissue. In the Chernobyl region, we know that the thyroid doses received by children peaked at 57 Gray in the region most heavily contaminated with radioactive iodine. In the same region (Gomel), 80% of children had doses between 0.18 and 5.4 Gray. Such doses were therefore unable to cause deterministic effects.
In fact, students have to realize that the main consequence of the Chernobyl accident is the induction of several thousands of thyroid cancers among children in the years following the accident.
The consequences of a contamination are usually stochastic effects (long-term effects of carcinogenesis) except for rare exceptions like the internal contamination of Litvinenko (alpha-emitter) or the external skin contamination when high radioactive concentration (e.g. beta burns by cesium 137 during the Goiania accident).

IRRADIATION AND SHORT-TERM EFFECTS

The difference between local and global irradiation has to be known.
In the context of a local irradiation, the main target of ionizing radiation is the skin, with a symptom that could be considered as a sentinel: the erythema (3-5 Gy). Necrosis can appear when the exposure is more important, at about 25 Gray. However, in case of a terrorist attack, erythema can be the silent witness of an unknown exposure to a radiological source and even if several irradiated wounded could see the same doctor, this practitioner could not give the alarm…
In the context of a global irradiation, deterministic effects could have a three weeks latency period and the consequences on hematopoietic organs are quickly important. Again, in case of a terrorist attack, that kind of diagnostic could be very difficult without any knowledge on the effects of ionizing radiation.

6. PRIORITY FOR THE TREATMENT

CONTAMINATION: TREATMENT IS AN EMERGENCY

Here, it should be remembered that the absorbed dose by a tissue is a cumulative phenomenon in time. Therefore, for an internal contamination, to limit the effects of ionizing radiation, decontamination has to be performed as fast as it is possible. Usually, this kind of treatment can't remove 100 % of the deposited radionuclides (**figure 1**). For an external contamination, decontamination can remove all or most of the contaminant and therefore its efficiency can be total.

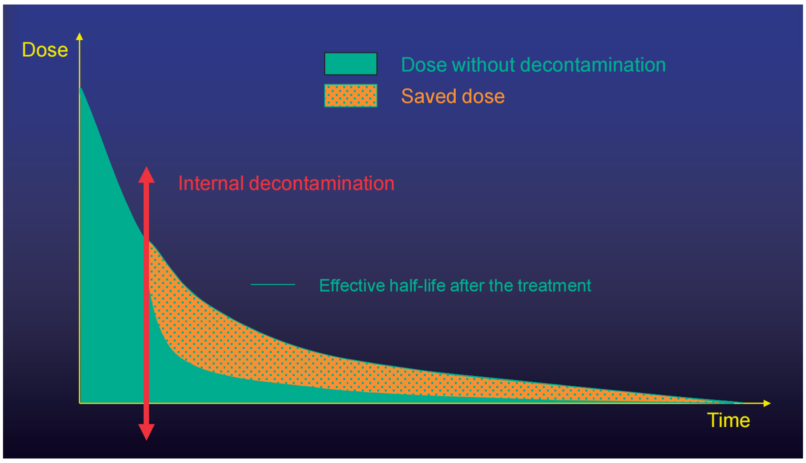

Figure 1. Effectiveness of internal decontamination < 100 %.

Even if the risks are late for internal or external contamination, the treatment is an emergency to minimize the committed dose for the victim.

IRRADIATION: ASSESSMENT OF THE DOSE IS AN EMERGENCY

In the framework of an irradiation, the treatment is not an emergency. On the contrary, assessment of the dose is the more important thing for the diagnosis, the prognosis and the treatment. Students have to understand that the reconstruction of the dose received by the victim will be impossible if a maximum of informations is not collected on the scene just after the accident.

One of the targets of our teaching is to provide practical information about good reflexes like removal from exposure, protection of people, alert and other actions especially for:

- clinical dosimetry: unspecific but very important symptoms like nauseas, vomiting, parotidis, convulsions… have to be underlined (**figure 2**);
- biological dosimetry with blood counts every four hours (decrease of lymphocytes correlated with the dose) and samples for cytogenetic dosimetry (dicentrics and rings).

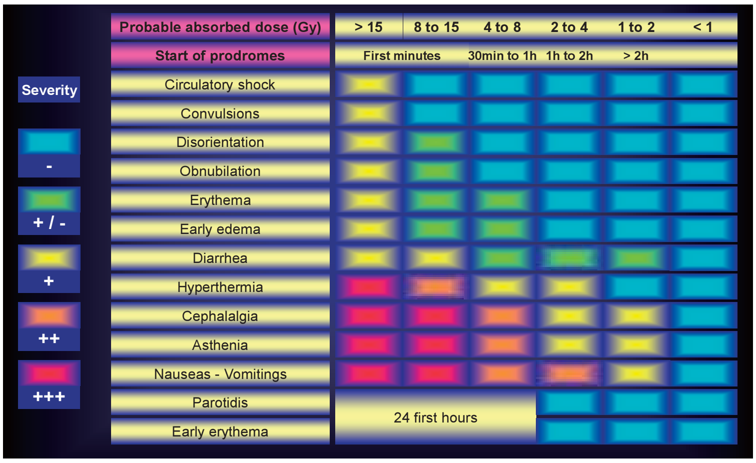

Figure 2. Clinical dosimetry.

7. TYPE OF MEDICAL MANAGEMENT

This part concerns the medical management that could be performed by nurses or medical practitioners in front of a radio-contaminated or irradiated wounded.

CONTAMINATION: MEDICAL MANAGEMENT IS QUITE EASY

Fortunately for the students, it is not necessary to know in detail the biological phenomena in the body of all radionuclides! On the other hand, some key points have to be perfectly understood. There is a simplified diagram of the circuits of the contaminants in the body (**figure 3**) with three possible doorsteps: the skin for external contamination, the gastro-intestinal mucous membrane (internal contamination by ingestion) and the alveolus (internal contamination by inhalation). The other compartments are the blood, the target tissues (e.g. radio-iodine and thyroid, strontium and bone, cesium and muscle mass…) and renal and digestive elimination.

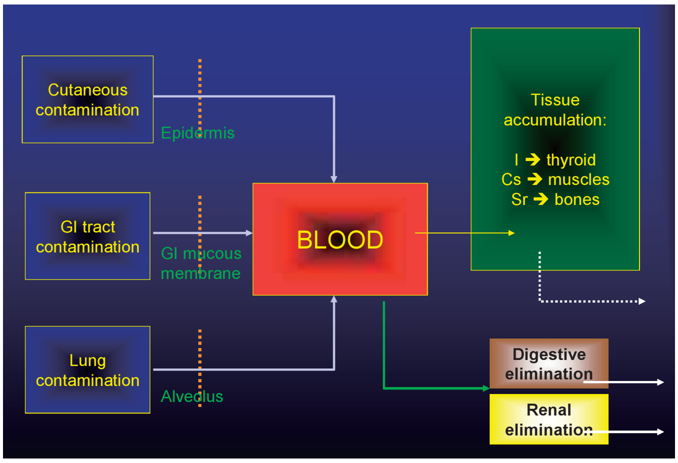

Figure 3. Simplified diagram of the circuits of the contaminants in the body.

It is important to remember that once it is accumulated in the target tissue, a contaminant becomes very difficult to remove. To keep in mind easily all the means used for the treatment of a radio-contaminated wounded, this diagram shows step by step the different available products.

At the doorstep
The skin is the first contact for a radionuclide. The contamination has to be removed quickly avoiding any injury (wound or burn) of the healthy skin to eliminate the risk of internal contamination. Simple means are used like water or soap. Undressing, in the framework of a special organization, is very efficient for trained team. DTPA (ampoules) could be use to irrigate the healthy skin and the wounds. At last, surgery would be efficient to remove contaminated and necrotic tissues.
When radionuclides are ingested, there are two complementary actions. The first is to avoid as much as possible their gastro-intestinal absorption. The simplest solution is to use bandages covering the gastro-intestinal mucous membrane (e.g. Gaviscon®). The second solution consits in accelerating the gastro-intestinal transit time to reduce the possible contact between contaminants and the intestinal mucous membrane (e.g. laxatives).
In case of a contamination by inhalation, bronchial washing is now prohibited. DTPA (powder or IV) is currently recommended as a chelating agent for plutonium and americium.

In the blood
Students have to memorize the two ways to accelerate the removal of radionuclides:

- the use of a chelating agent (e.g. IV DTPA – ampoules of 1 gramme);
- the use of a diluting agent: for example, the water cycle in the body is about 12 days, in case of a contamination by tritium, the treatment is very easy; the patient must drink three to four liters of water per day to reduce the duration of this cycle to three days only.

In the target organs.
The best situation is to treat the patient when the physiology of the body allows it, before the contamination itself. The example of potassium iodine illustrates this benefit. Stable iodine will saturate the thyroid tissue and thus will prevent any possibility of accumulation of radioactive iodine. The existence of two kinds of potassium iodine tablets (adults or children) must be known by the medical practitioners and the nurses.

Renal and digestive elimination
We saw that one of the targets of the treatment of an internal contamination was to accelerate the elimination of the radioactive contaminants. Therefore, two examples can be given during our teachings concerning digestive and renal elimination:

- the treatment of the contamination by uranium with an IV combination of acetazolamide and bicarbonate that will increase the renal filtration of uranium and block its tubular re-uptake;
- the treatment of a digestive contamination by laxatives or by Prussian Blue that trap the cesium in the intestines.

After this quick review, we can see that there are various products for the treatment of a radiological contamination. These therapeutic agents are characterized by rare contra-indications and adverse effects. Consequently, first treatment should be administered as fast as possible and blindly. If the radionuclide is not identified, all the available products could be administered in front of a victim suspected of contamination, i.e. any wounded person or without a facial protection found in the radiological area.
The start of the treatment should be performed in the same time as radiochemical samples (urines, feces, nasal swabs) which will confirm later the reality of the contamination and assess its importance. After a very efficient external decontamination, a whole body counting or a thyroid counting is always interesting.
In practice, the treatment is kept until the results of the laboratory or whole body counting. In case of a confirmation of the contamination, the posology will be adjusted to these new data.

IRRADIATION: A SPECIALIZED MEDICAL MANAGEMENT

For a local radiation burn, biological mechanisms depend directly on which kind of organs or tissues are concerned. However, one organ is systematically involved in all accidents: the skin. Radiation injuries could give an idea for the assessment of the dose (**table I**), from an erythema (skin dose from 3 to 5 Gy) until skin necrosis (dose > 25Gy). The Percy military hospital has a huge experience in the management of such a patient and that is a great opportunity for our students. Our new therapeutic approach combines surgery (after a dosimetric reconstruction) and local stem cell therapy. We believe that this innovative treatment could improve the evolution of local radiation burns in term of functional and vital results.

Table I. Assessment of the dose for a local radiation burn.

Dosis (Gy)	**Effects**
> 25	*Skin necrosis*
> 20	Ulceration
> 15	Moist epithelitis
> 6	Dry epithelitis
> 4	Depilation
3 – 5	*Erythema*

General effects of whole-body irradiation can only be imagined in the case of high energy radiation sources like those used for radiotherapy. A whole-body irradiation with an average or high dose will produce a mixed pathology involving the haematopoietic system, the gastro-intestinal tract or the neurovascular system. An early clinical examination (associated with blood counts) will help to assess the degree of exposure. The most important message for the students about the treatment is to realize that the bone marrow graft is an exceptional therapeutic, always deferred to three weeks: growth factors and hematopoietic stem cells are nowadays the gold standard.

8. RISKS FOR THE MEDICAL CREW

Any medical intervention with a radio-contaminated or irradiated wounded must be made with reasonable safety for personnel.

CONTAMINATION: PROTECTION OF THE MEDICAL CREW IS NEEDED

In case of an external or internal contamination, a person close to the victim will be exposed to ionizing radiation. For an internal contamination, an example like the complete isolation of the patients treated with high activities of 131 iodine (gamma radiation) could be given to the students. For an external contamination, the risk is the direct transfer of the radionuclides from the victim to the nurse or the medical practitioner.

Therefore, the protection of the medical crew could be, in the hospital, clothes like a TYVEC® with a surgical mask and double gloves. The level of protection would be more important on the radiological area with heavy clothes and breathing apparatus.

However, these precautions do not protect against the risk of irradiation. Indeed, time of intervention and a correct use of an electronic dosimeter with alarm would be the best solution.

IRRADIATION: NO SPECIAL PROTECTION

No special protection is needed in front of an irradiated wounded with the exception of the intervention where a source may cause a risk of external exposure. An irradiated patient does not irradiate.

In conclusion, the medical management of a radio-contaminated or irradiated wounded depends on simple principles modulated by the severity of injuries and the type of exposure. These principles would be the minimal basic knowledge in case of a major accident, especially in front of:

- a huge number of wounded;
- a panic reaction;

- a complete disorganization of emergency aid.

Our teaching underlines the differences in the management of such patients highlighting paradoxes (**table II**). With a radio-contaminated wounded, protection of the medical crew is needed but the medical management is quite easy. The consequences of a radio-contamination are usually long-term effects (carcinogenesis) and, on the contrary, treatment is an emergency. No special protection is needed in front of an irradiated wounded and there's a true contrast with the treatment which needs specialized and innovative techniques. The consequences of an irradiation are usually short-term effects (deterministic effects) and the assessment of the dose is an emergency: it will determine the therapeutic strategy and the prognosis.

Table II. Management of a radio-contaminated or irradiated wounded: contrasts and paradoxes.

Contaminated wounded		**Irradiated wounded**
Long-term effects	***Radiological risks***	Short-term effects
Treatment = emergency	***Priority for the treatment***	Dose assessment = emergency
Quite easy	***Medical management***	Specialized medical management
Protection of the medical crew	***Risks for the medical crew***	No special protection

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Rehabilitation in acute burn radiation syndrome: Experience of Percy army hospital

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Keywords: radiation burn, dosimetry, surgery, Cellular therapy, mesenchymal stem cells; rehabilitation; physical therapy; occupational therapy

The therapeutic management of severe radiation burns remains a challenging issue today. Radiation burn is a determined effect of localized irradiation, and the lesion is in good correlation with absorbed radioactive dose. Radiation burns are very different from thermal burns. The evolution is spatiotemporally unpredictable and hardly controllable, with successive inflammatory waves and recurrence of fibro-necrosis process that conventional surgical treatment (including excision, skin autograft, or flap) fails to prevent. Each surgical operative treatment even seems to stimulate inflammation and fibro-necrosis process. Unfortunately the lesion often evolves towards amputation or disjointing and even death.

In a recent very severe accidental radiation burn we demonstrated at Percy military hospital the efficiency of a new therapeutic approach combining surgery and local cellular therapy using autologous mesenchymal stem cells (MSC). We also confirmed the crucial role of the dose assessment in this medical management. For five years now, cell therapy has been an adjuvant treatment of surgery. This combination is a therapeutic innovation along with the recommendation for conservative surgery in serious radiation burn.

Regarding rehabilitation we describe here with the example of 2 patients the functional consequences of radiation burn. They are different from thermal burn injury: no hypertrophy bridles or paraosteoarthropathy but severe stiffness of joints. In this case physical and occupational therapy are very important and we describe here the different techniques used.

The first patient presented a very important radiation lesion located on the arm, first treated by several surgical procedures: iterative excisions, skin grafts, latissimus dorsi muscle flap, and forearm radial flap. This conventional surgical therapy was unfortunately inefficient, leading to the use of an innovative cell therapy strategy based on autologous MSC. A total of five local MSC administrations were performed in combination with skin autograft. After these iterative local MSC administrations, the clinical evolution was favorable and no recurrence of radiation-induced inflammatory process occurred during the patient's 8-month follow-up. The benefit of this local cell therapy could be linked to the ''drug cell'' activity of MSC by modulating the radiation inflammatory processes, as suggested by the decrease in the C-reactive protein level observed after each MSC administration. This procedure allowed a good and stable reconstruction of soft tissues of the arm with both a relief of pain and absence of cutaneous necrosis relapse. Sequelae were limited to functional and cosmetic after-effects. A limitation of joint amplitudes was also found. The abduction of shoulder and the extension of the forearm were limited, respectively, to 0–45 and to 45–90. Furthermore, the active extension of the wrist and hand was impaired, while flexion and sensation were preserved. Today, with a 3 year follow-up there has been no recurrence of lesions.

The second patient presented an important radiation burn located on both hands. After surgical and stem cell therapy he presented stiffness of the fingers and the wrist. Exercises of Rehabilitation are described in this case.

CONCLUSION

The success of this combined treatment suggests a new perspective in the medical management of severe radiation burns and more widely in the improvement of wound repair. But the functional consequences and the importance of rehabilitation in acute radiation burns are rarely described in the literature. Their mechanism except for the skin and the muscles in term of tendons or joint diseases are unknown and open to future possibility of research.

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Quality of Life and problems in daily living of patients who receive radiotherapy

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Abstract: The aim of this study was to clarify the status of QOL and problems in daily living of patients who undergo radiation therapy, based on the type of radiation, site of irradiation, dosage, dose rate, method of irradiation, and various clinical data. Subjects were inpatients and outpatients receiving radiation therapy at Hirosaki University Hospital. The patients were asked to record problems in daily living using a symptom diary from the day before the start of radiation therapy until its completion. Clinical data and QOL were collected before irradiation, during irradiation, at the end of irradiation, and 4–6 weeks after the end of irradiation. Data collection began in July 2010.

Key words: Radiotherapy, Quality of Life, Symptom diary, Nursing care

Introduction

Radiotherapy is an effective method for cancer treatment. However, because radiation harms normal cells and tissues, adverse effects occur in patients who receive treatment. Symptoms of acute radiation damage, particularly general malaise, hair loss, oral inflammation, and diarrhea, cause patients distress. Supportive care is given to patients who present with these symptoms, but no effective nursing care has yet been established. If the status of QOL and problems become clear in daily living experienced by patients depending on the site and method of irradiation would provide, new suggestions for the development of future nursing care.

Study aims

The aim of this study was to clarify the status of QOL and problems in daily living of patients who undergo radiation therapy, based on the type of radiation, site of irradiation, dosage, dose rate, method of irradiation, and various clinical data.

Plan of this study

2009：The arrangement about a study program

It was performed at Hirosaki University School of Medicine and Hospital, and Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Sciences (NIRS).

2010 and 2011：Data collection

2012：Society announcement, Paper creation and contribution

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Methods

***Subjects*:** Inpatients and outpatients receiving radiation therapy at Hirosaki University School of Medicine and Hospital. Full explanations are being given to all subjects, and all patients are being asked for their informed consent.

Problems in daily living : The patients were asked to record problems in daily living using a symptom diary by making daily entries in the diary between the end of the evening meal and bedtime, from the day before the start of radiation therapy until its completion. The symptoms written in the diaries were classified as Grade 1 – Grade 5 according to the Common Terminology Criteria for Adverse Events v3.0, Japanese translation JCOG/JSCO. Six kinds of symptom diary were prepared according to the irradiated site. They were for the breast, the lung, the pelvis, the upper gastrointestinal tract, the lower gastrointestinal tract, and the eye. A sample of symptom diary was shown in Fig 1.

Clinical data: Data on RBC, WBC, lymphocytes, granulocytes, Hb, platelets, TP, and Alb, as well as type of radiation, site of irradiation, dosage, dose rate, and method of irradiation, were collected from the patients' records. The data were collected before irradiation, during irradiation (each week), at the end of irradiation, and 4–6 weeks after the end of irradiation.

Patient's Name ____________________

Date of hospitalization ____________

Date of irradiation starting ____________

Site;Breast

		Sun.	Mon.	Tues.	Wed.	Thurs.	Fri.	Sat.
Date		/	/	/	/	/	/	/
Irradiation days		Before	1	2	3	4	5	
Symptoms and strength	**General malaise**							
	Loss of appetite							
	Nausea							
	Vomiting							
	Loss of weight							
	Dermatitis							
	Itching							
	Pain（Site　　　）							
	Pain（Site　　　）							
If you have troubled, please write symptoms.								

Fig.1 Symptom diary

QOL: The SF-8™ standard version was used. This scale consists of 8 domains of physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health, and its reliability and vitality have been confirmed. Comparisons with national standard values by sex and age group are possible. The survey will be conducted 3 times: at the time of admission or outpatient examination, at the completion of radiotherapy, and 4-6 weeks after the completion of radiotherapy.

Survey period: July 2010-March 2012

Study status

This study was approved by the research ethics committee of Hirosaki University Hospital in June

2010 (approval no. 2010-011), and data collection began in July 2010. Data by the present was showed in table 1.

Table 1 Data by the present

Total subjects	n=26	
Age	21 years～82 years	
Sex	Male 14 Female 12	
Site of irradiation	Pelvis	8
	Prostate	4
	Ovary	2
	Others	2
	Breast	8
	Lung	7
	Eye	2
	Neck	1
Dosage	10Gy～74Gy	

Activities of public health nurses in preparation for nuclear disaster
- Health centers and local government -

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Abstract: This research aimed to clarify the present status of health care preparedness for a nuclear disaster.In fiscal year 2009, 124 institutions comprising all of the prefectural health centers in cities, towns, and villages in prefectures with nuclear installations and the two adjoining prefectures were included in the investigation. A questionnaire survey was conducted of the public health nurses in charge of health-crisis management in each center. The response rate was 71.8%.
Two local governments and five health centers had participated in an emergency nuclear disaster drill. The role of the public health nurse in local governments was providing guidance during resident evacuation in the event of a nuclear accident. The health center public health nurse was responsible for carrying out tasks including providing verbal consultation at a first-aid station, health consultation, and decreasing anxiety.It seems that there is a clear division of roles in affiliated institutions for emergency nuclear disaster drills. However, it will probably be necessary to develop activities according to residents' needs.

Keywords：Radiation disaster, Public health nurse, Health Crisis management , Preparation

Purpose

This study aimed to clarify the current state of readiness for nuclear disaster, based on the public health activities of local governments and the perceptions of public health nurses.

Method

In a 2009 survey, a questionnaire survey was conducted of public health nurses responsible for health crisis management at prefectural public health centers and all 124 municipalities in a prefecture in which a nuclear power plant was located, and 2 neighboring prefectures. Eighty-nine survey forms were collected, for a response rate of 71.8%. The response rate was 69.6% in the prefecture with a nuclear power plant, 74.3% in Prefecture B, and 72.1% in Prefecture C. No bias was seen.

Questionnaires were sent by mail, with a request to managers at each facility to select the respondent. The survey was conducted in October-November 2009.

The main questionnaire items included whether or not there were training classes for public health nurse activities for times of disaster, and whether or not this training included radiation (atomic energy) disasters.

A written explanation was provided of the study's purpose, including that the study would be anonymous, that local government organizations could not be identified, and that responses would be processed statistically. Return of the survey form was taken as consent.

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Results

1. Subjects' basic attributes

1) The subjects' mean age was 49.8 years. More than half had 26 years of experience and a position of section head or higher; thus, the responses were from veteran public health nurses.

2) Thirty-two responses were obtained from the prefecture with the nuclear facility, and 57 responses from prefectures B and C.

2. Emergency drills for radiation disasters

Two municipalities and five public health centers participated in emergency drills for radiation disasters (Table 1). Responses were obtained from 6 facilities on the roles of public health nurses in such disasters.

1) Role of municipal public health nurses:

Evacuation guidance

2) Role of health department public health nurses:

Medical interviews, health consultations, monitoring of health status, confirmation of actions at the time of the disaster and physical condition, reduction of mental anxiety

3. Training for radiation disasters

Two municipalities and two public health centers sent public health nurses to training workshops on radiation in 2009 (Table 1). All four of these facilities were located in the prefecture with the nuclear power plant. In 2010, only one municipality, located in the prefecture with the nuclear power plant, plans to send a nurse to a training workshop.

Table 1. Preparedness for radiation disasters

		Yes	No	No resp.	Total
Emergency drills	Municipality	2	59	8	69
	Pub. health ctr.	5	15	0	20
	Total	7	74	8	89
Sent people to training workshops in 2009	Municipality	2	60	7	69
	Pub. health ctr.	2	18	0	20
	Total	4	78	7	89
Plan to send people to workshops in 2010	Municipality	1	64	4	69
	Pub. health ctr.	0	20	0	20
	Total	1	84	4	89

Consideration

1. Investigation of normal response making use of emergency drills

According to Article 13 Paragraph 1 of the Act on Special Measures Concerning Nuclear Emergency Preparedness, the national government, prefectures, and municipalities should participate in integrated training for nuclear disasters. According to disaster guidelines, emergency planning zones (EPZ) are considered to be about 8–10 km around nuclear power plants and 5 km around nuclear fuel reprocessing plants. Therefore, the area around facilities at which a disaster may occur that is covered by disaster training facilities is thought to be small. According to the Basic Plan for Disaster Prevention (Nuclear Disaster Measures), the national government is required to conduct general drills once a year, and local public bodies and nuclear power companies are required to conduct regular disaster drills for each aspect of disaster activities. These drills must be arranged so as to be specific and practical. Participation in drills even once a year is a valuable opportunity for simulation.

In disaster drills, public health nurses have distinct responsibilities depending on the organization to which they belong. In the JCO accident, however, municipal public health nurses and public health center nurses formed pairs and were involved in a wide range of activities, from maintaining life in evacuation centers to providing health consultations.1) This indicates the need for cultivation of the ability to be creative and conduct a wide range of activities suited to the situation at the time, on the assumption that things will not always go according to the manual. The attitude of public health nurses toward emergency drills is therefore important, with the major premise that they will acquire basic knowledge of radiation in advance.

Even with participation in drills, it is predicted that differences will appear in systems that are being prepared for contingencies, depending on whether or not participants have previously acquired knowledge. These differences will appear in areas such as role awareness or discovering points to improve. Drills are also an occasion for participants to notice what needs to be done at regular times. Public health activities are thought to function effectively based on the preparation of specific measures during normal periods, with drills as an opportunity to apply these measures.

2. Need for training for public health nurses

In daily efforts to prevent disasters, public health nurse activities that may be lacking include dealing with citizens from a position of knowledge, having a long-term outlook, and the ability to determine what emotional care measures are needed at present. Among these daily tasks, it is important that nurses receive training to supplement these areas that are lacking. From description which checked the hope about training of question paper, we can gain an idea of the current situation in which people receive training while their roles in emergencies remain vague.

Necessity and feasibility of rehabilitation for patients exposed to radiation

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Abstract The purpose of this study is to explore necessity and possibility of rehabilitation for patients exposed to radiation by reviewing historical patients in radiation accidents from a viewpoint of rehabilitation. The reviewing study has shown that the report of rehabilitation for patients exposed to radiation is only one, the case of JCO accident. In this patient, the range of motion exercise was performed to impairments derived from radiodermatitis and skin transplantation, and also aspiration pneumonia caused by oral mucosal exfoliation was treated by respiratory rehabilitation. In the other radiation accidents, there were many patients with radiodermatitis, but there was no patient who received rehabilitation therapy. Although, intervention such as a range of motion exercises to these patients seems to be effective because skin transplantations were performed just like usual severely-burned patients. From the reviewing in this study, it was suggested that rehabilitation for patients exposed to radiation is effective in general support such as a range of motion exercises for skin transplantation and respiratory rehabilitation for aspiration pneumonia. However, because the case of rehabilitation for patients exposed to radiation is a very rare and fundamental study is poor, it is still difficult to create a guideline for decision making in this area. The challenge for the future is to show an evidence of effect in rehabilitation for patients exposed to radiation by considering a pathological animal model.

Key Words: radiation exposure; rehabilitation; radiation burn; respiratory rehabilitation

Introduction

The many atomic energy-related institutions are located in Aomori. Accordingly, it is essential to develop a system of radiation emergency medicine in the unlikely event of an accident in one of these facilities. In this system, physical therapists and occupational therapists should perform interventions focusing on rehabilitation for residual disability derived from an accident. However, there are very few reports regarding the delivery of rehabilitation for patients exposed to radiation, and it is uncertain which interventions are effective. Consequently, the purpose of this study was to explore the necessity and feasibility of rehabilitation for patients exposed to radiation.

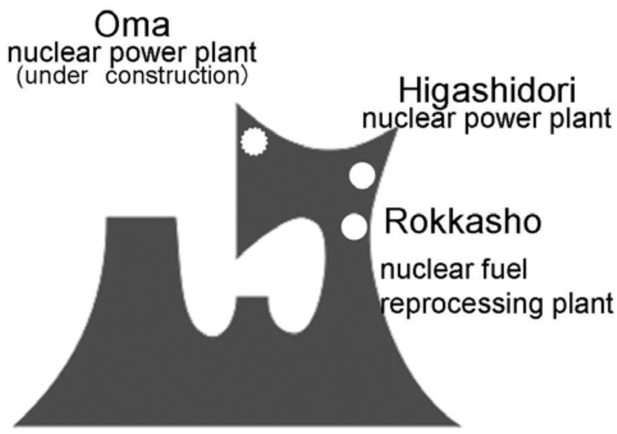

Figure1.: Atomic energy-related establishments in Aomori

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This study investigated the medical treatment target of the rehabilitation of patients with radiation exposure by reviewing data from historical reports from victims of radiation accidents from the viewpoint
of rehabilitation. We searched PubMed for English literature and Ichushi (Japana Centra Revuo Medicina) for Japanese literature. The search term was "whole body radiation expose（全身被ばく）", "regional radiation expose（局所被ばく）", "acute radiation syndrome（急性放射線障害）", "internal radiation radiology (IVR)", "non destructive inspection（非破壊検査）", "radiation burn（放射線熱傷）" and "respiratory rehabilitation（呼吸リハビリテーション）". Because generally, "internal radiation radiology (IVR)", "non destructive inspection（非破壊検査）" and “respiratory rehabilitation（呼吸リハビリテーション）" did not show a radiation exposure-related matter, we added "radiation expose（被ばく）" respectively. In addition, we added "rehabilitation（リハビリテーション）" to the keyword mentioned above for the extraction of the medical treatment target of the rehabilitation. The search period of Ichushi was set from 1983 to 2010 (all years).

Results

1. Status of the related previous studies

A review of the literature identified only one report of rehabilitation for patients exposed to radiation, which described the treatment of a victim of the JCO accident [1-3]. In this patient, range of motion exercises (ROMex) were performed for impairments derived from radiodermatitis and skin transplantation, and aspiration pneumonia caused by oral mucosal exfoliation was treated by respiratory rehabilitation. Although other radiation accidents have caused many cases of radiodermatitis, rehabilitation therapy for such patients has not been reported before or after the JCO accident.

For the accident case that there was not intervention of the rehabilitation, it was described about a place and the process that occurred of the radiation exposure accident, but there was not mention of the medical treatment to patients with radiation exposure. Also, there were few examples exposed to radiation with a large dosage to the whole body. Whereas some reports were found about regional radiation expose [4-6]. The thing which there was many was caused by field of industry used radiation material such as Non-Destructive Inspection in these reports. In late years there was much radiation exposure of the medical scene with testing, the medical treatment using the radiation such as the IVR. In the case of regional radiation expose, skin transplantation was performed similar to a case of Thermal burn for the site which produced radiation burn. From results of the document retrieval of the victim of these past radiation exposure accidents, as for the medical treatment target of the rehabilitation, patients with radiation exposure included radiation burn and a respiratory function.

２. About radiation burn

Radiation burn is a skin disorder resulting from radiation exposure. Radiation burn and thermal burn are the symptom to develop in skin is similar, whereas the course is completely different to show it in Figure2 [7,8]. Thermal burn is injured in the skin surface, and severity and a range are determined in a few days. However, radiation burn has decreased mitotic activity of cells by the DNA lesion of the epidermal basal layer occurring by radiation exposure and gradually worsens in turnover of the tissue in total. Therefore it is difficult to do a prognostic value just after the radiation exposure, and it becomes important that we evaluate a radiation dose appropriately.

Left：Thermal burn　Right：radiation burn (Adapted from the burn treatment manual and Acute medical management of radiation accident victims)

Figure2.

The difference between Thermal burn and radiation burn

３. About respiratory condition of extensive radiation-exposed patients

The gas exchange is important to a life support in air vesicle. It is necessary to make thoracic cavity negative pressure by thoracic expansion and a diaphragmatic shrinkage so that air makes it flow in in lung. It is necessary to push air by relaxing with thoracic reduction and diaphragm so that lung produces air. Thus, a chest and the diaphragmatic movement enable a gas exchange with the air vesicle by making air go in and out of lung.

For patients with severe radiation exposure, thoracic range of motion decrease is caused by radiation. And haemorrhage of digestive tract and the dysperistalsis with the radiation cause abdominal distension[5]. The abdominal distension pushes up diaphragm and disturbs thoracic movement. Furthermore, when it is placed under artificial breathing management, thoracic spontaneous movement decreases, and the thoracic range of motion decrease is promoted. Also, pneumonia is exacerbated by increase of the intraoral mucosal exfoliation and sputum more.

Discussion

From reviewing the JCO accident study [1-3], it was suggested that rehabilitation for patients exposed to radiation is an effective form of general support, with examples including ROMex for skin transplantation after radiation burn and respiratory rehabilitation for aspiration pneumonia. Therefore we think about necessity and feasibility of the rehabilitation about each.

１. Necessity and feasibility of rehabilitation for radiation burn

In late years, as a result of this study, many things were caused by testing, medical treatment to use the radiation such as the IVR in a medical scene in a report of radiation burn [4-6]. Guidelines are considered about the radiation burn with the IVR, and medical treatment such as debridement or the skin transplantation is chosen similar to a case of thermal burn. However, I was not able to see the thing mentioned about a thing of subsequent rehabilitation. In the case of thermal burn, it is shown that the rehabilitation such as ROMex and streching, splinting is effective for the flexibility of the skin grafting part and mobile acquisition after debridement and skin transplantation [8-11]. Therefore, it is predicted that these rehabilitation treatment is necessary when it is taken debridement and skin transplantation after a radiation burn. These rehabilitation treatments is provided for the victim of the JCO accident, and the intervention of the rehabilitation for radiation burn is thought to have possibilities to expect some effect because some effect was found [2-3].

２. Necessity and feasibility of respiratory rehabilitation in respiratory management for extensive radiation-exposed patients

For patients with severe systemic radiation exposure, it is an important problem to maintain a respiratory function while the patients lie in bed. There is the risk to accompany the aspiration pneumonitis by oral mucosa being affected by radiation when exposed to radiation. Also, there is the risk that oxygen concentration of the blood decreases from the chest and the diaphragmatic mobile decrease, fibrosis of the lung by radiation. In addition, the patients under the artificial breathing management cause the decrease of the respiratory function by a reduction in thoracic mobility more. Under these situations, it is necessary for the therapist to maintain the thoracic mobility and give the changing position to promote discharge of the sputum. Because these presented with some effect by having been performed for the victim of the JCO accident, it is predicted that we can expect some effect [1,3]. Also, for the patients exposed to radiation severely widely, the patients are at increased risk for suffering from aspiration pneumonitis by the decrease of the immune function and exfoliation of the oral mucosa. In contrast, it seems to be necessary to give mouth care from an early stage.

３. The challenge for the future

The cases of rehabilitation for patients exposed to radiation are very rare, it remains difficult to create a guideline for decision making in this area. The challenge for the future is to find evidence of effect in rehabilitation for patients exposed to radiation, which could be achieved using an animal model of the pathological processes involved in radiation injury.

Acknoledgement

The authors thank Dr. Masahiko Kimura from Kitasato University for his valuable comments. This research was supported by a grant from the Hirosaki University Graduate School of Health Sciences Radiation Emergency Medicine Human Resource Cultivation Project.

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Evaluation of educational planning and implementaion of human resource development after Radiation Emergency Medicine

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This year, we were starting education program to undergraduate first year students, postgraduate master course and incumbent course for nurses and radiological technologists. For the development and validation of these programs, we investigate to audience to use some questionnaires. The purpose of this study is to clarify the effect of these educational programs. In addition, to clarify the demand for professionals of radiation emergency medicine in enterprises and organizations.

Methods: .1) Developing questionnaires: From previous studies, some articles related to educational effects but no concern radiation emergency medicine professionals.

2) Pilot study: Last year we did to investigate the needs of the professionals of radiation emergency medicine in several Nuclear power plants.

3) Undergraduate and postgraduate students, pertaining to health care for the incumbent, the educational program was planned to investigate whether the plan is attractive and would receive education in 2010 undergraduate, postgraduate education, training conducted at the start of the incumbent was to examine the effect at the end.

4) Continue to investigate and demand for human resources and skills needed to be accepted as the employers of graduates of the School of Radiation Emergency Medicine Training.

Result: From pilot study, we found some questions and also need our policy and materials to send these facilities. Developing questionnaires, I continue to develop and validation these questionnaires.

This year, I will start these studies, so I will prepare to accept to research ethics committee of Hirosaki University Graduate School of Medicine and Hospital.

Management of disaster prevention and disasters in home-visit Nursing Stations in prefectures with atomic facilities

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Abstract The purpose of this research was to clarify the present status of disaster prevention and provision of assistance in cases of disasters involving nuclear accidents at home-visit nursing stations, as well as home-care nurses' perceptions of them. The questionnaires included the characteristics of the home-visit nursing stations, readiness for disaster prevention, and provision of assistance for disasters at the home-visit nursing station and the network system, home-care nurses' perception and consciousness of the problems of disaster prevention and provision of assistance for disasters at the home-visit nursing station. Surveys were distributed by mail to 402 directors of home-visit nursing stations in prefectures with atomic facilities located north of Kanto. A total of 96 (23.9%) surveys was completed and returned. Directors showed very limited knowledge of nuclear accidents in their home-visit nursing stations, needed knowledge and preparation, and were unclear about the handling of nuclear accidents. The research identified community differences in the sense of concern about nuclear accidents.

Keywords: disaster prevention, nuclear accident, home-visit nursing,

Introduction

Due to reductions in the length of hospital stays, patients more frequently receive medical care at home. The number of outpatients who depend on medical care has gradually increased as the home care system and clinical devices have continued to improve. Consequently, the number of home care nurses has also increased. Despite the need for home-visit nurses, various problems with the system remain. It is difficult for small-scale and pragmatic businesses to continue to manage home-visit nurses. However, as nurses can most accurately monitor patients' conditions and maintain confidential relationships, outpatients who depend on medical care should receive home-visit nursing support. The history of home-visit nursing is short; therefore, the home care system is poorly equipped, and some of the pragmatic business facilities that conduct home-visit nursing only consult the manual for how to prevent disasters and formulate disaster response plans. Consequently, it is important to evaluate the current disaster prevention plans and systems for providing assistance during a disaster, including a nuclear accident. Home-visit nurses would be able to address the challenge and become increasingly aware of disaster prevention if we were to conduct a survey of the current disaster prevention plans and systems for providing assistance during disasters at home-visit nursing stations. Finally, it is hoped that disaster prevention plans will be unified across Japan.

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Purpose

The purpose of this research was to clarify the present status of disaster prevention and provision of assistance in cases of disasters involving nuclear accidents at home-visit nursing stations, as well as home-care nurses' perceptions of them.

Methods

The questionnaires included the characteristics of the home-visit nursing stations (community, scale, employees, and outpatients), readiness for disaster prevention, and provision of assistance for disasters at the home-visit nursing station and the network system, as well as home-care nurses' perception and consciousness of the problems of disaster prevention and provision of assistance for disasters at the home-visit nursing station. Surveys were distributed by mail to 402 directors of home-visit nursing stations in prefectures with atomic facilities located north of Kanto: 138 directors in Hokkaido, 44 in Aomori, 63 in Miyagi, 59 in Fukushima, 57 in Ibaraki, and 41 in Niigata. A total of 96 (23.9%) surveys was completed and returned. As appropriate, the chi-square test or the Kruskal Wallis test was used for analysis of differences. All statistical analyses were performed with SPSS 16.0 J for Windows with the significance level set at $p<0.05$.

The research was approved by the Research Ethics Committee of the Graduate School of Health Sciences, Hirosaki University (2009-150).

Table 1 Directors' perceptions of knowledge of nuclear accidents in home-visit nursing stations

		Average	Standard deviation	Conditioned residual error			Significance level
				Think so	Yes and no	Don't think so	
1	I am aware of the Special Fiscal Measures for nuclear accidents.	1.38	0.90	−26.0	−16.0	42.0	***
2	I know about the prevention of nuclear accidents.	1.24	0.72	−27.0	−20.0	47.0	***
6	I know about nuclear accidents.	1.43	1.03	−24.0	−18.0	42.0	***
14	I know the medical system for nuclear accidents.	1.45	0.95	−26.0	−13.0	39.0	***
16	I know the role of home-visit nurses during nuclear accidents.	1.45	0.95	−26.0	−13.0	39.0	***
18	I know who has the primary responsibility, such as a task force, during a nuclear accident.	1.50	1.11	−23.0	−17.0	40.0	***
19	I know the location of where to respond to nuclear accidents.	1.31	0.85	−26.0	−19.0	45.0	***
20	I know the prefecture-wide response to nuclear accidents.	1.33	0.87	−26.0	−18.0	44.0	***
4	I know that prefecture-wide disaster drills are conducted for nuclear accidents.	2.17	1.65	10.0	−15.0	25.0	***

chi-square test, n=84, ***;<0.001

Table 2 Directors' perceptions of need for knowledge of nuclear accidents and a sense of crisis in home-visit nursing stations

		Average	Standard deviation	Conditioned residual error			Significance level
				Think so	Yes and no	Don't think so	
3	I think that knowledge of prevention of nuclear accidents is necessary.	3.90	1.53	24.0	−10.0	−14.0	***
7	I think that knowledge of nuclear accidents is necessary.	4.07	1.54	31.0	−17.0	−14.0	***
2	I think that knowledge of nuclear accidents is necessary in the medical system.	3.95	1.63	29.0	−18.0	−11.0	***
22	I think that knowledge of the effects of radiation exposure is necessary.	4.19	1.49	35.0	−20.0	−15.0	***
5	I think that participation in disaster drills for nuclear accidents should be mandatory across the prefecture.	2.93	1.40	−9.0	15.0	−6.0	**
24	I think that nuclear accidents should include not only weapons and accidents in atomic facilities but also terrorism.	3.48	1.41	5.0	10.0	−15.0	**
9	I recognize that eliminating nuclear accidents is practically impossible.	2.38	1.35	−18.0	10.0	8.0	***
15	I feel a need for preparation of nuclear accidents.	3.26	1.58	4.0	3.0	−7.0	n.s
8	I feel a sense of crisis regarding nuclear accidents.	2.79	1.58	−6.0	3.0	3.0	n.s

chi-square test, n=84, ***; p<0.001, **; p<0.01

Results

The number of respondents who indicated: "I have a clearly-stated policy for preventing nuclear accidents" was 3 (3.1%); "I do not have a clearly-stated policy for preventing nuclear accidents" was 79 (82.3%); "Don't understand" was 11 (11.5%); and "No response" was 3 (3.1%). The respondents who indicated that they have a policy were from Fukushima (1 respondents) and Miyagi (2 respondents).

The number of respondents who indicated: "I have participated disaster drill for a nuclear accident" was 2 (2.0%); "I have not participated" was 86 (89.6%); "Don't understand" was 4 (4.2%); and "No response" was 4 (4.2%). Respondents who indicated participation in a disaster drill were from Ibaraki and Miyagi (1 respondent each). The number of respondents who indicated: "I have an advertisement for preventing nuclear accidents" was 2 (2.0%); "I don't have an advertisement for preventing nuclear accidents" was 86 (89.6%); "Don't understand" was 4 (4.2%); "No response" was 4 (4.2%). Respondents who indicated that they had an advertisement were from Aomori and Miyagi (1 respondent each). All of the above were significantly different (chi-square test, $p<0.0001$).

Significant differences were observed for all items ($p<0.0001$). The questionnaire contained 24 items regarding perceptions of nuclear accidents evaluated on a 5-item scale. The 5-item response scale was changed to a 3-item scale to simplify the response distribution. Re-analysis was conducted using the 3-item scale.

There were significant differences among prefectures at the 5% level using the Kruskal-Wallis test. Prefectures in which the participants had the highest sense of concern about nuclear accidents were Aomori, Niigata, and Fukushima. Prefectures in which the participants were most likely to perform expected home visits unless they were in areas that were off-limits area during a nuclear accident situation were Niigata, Fukushima, and Hokkaido. There was a significant difference in concern about nuclear accidents on the 3-item scale ($p<0.05$). There was no significant difference among the types of facility.

Table1 showed directors' perceptions of nuclear accidents in home-visit nursing stations. Directors had very limited knowledge of nuclear issues and the way to handle nuclear accidents; therefore, they need to have knowledge and preparation about nuclear issues and the way to handle nuclear accidents.

Table 2 shows the directors' perceptions of their need for knowledge about nuclear accidents and the sense of crisis in the home-visit nursing station. "I think that knowledge is necessary" was the most frequent answer. "I do not recognize that eliminating nuclear accidents is practically impossible" was also a frequent answer.

Table 3 shows the directors' perceptions of handling nuclear accidents in home-visit nursing stations. It is difficult to handle nuclear accidents without confirmation of the safety of patients. On the other hand, "I will visit patients' homes during a nuclear accident except in areas that are off-limits"

Table 3 Directors' perceptions of handling nuclear accidents in home-visit nursing stations

		Average	Standard deviation	Conditioned residual error			Significance level
				Think so	Yes and no	Don't think so	
10	I think it will be difficult for me to handle patients during a nuclear accident.	3.81	1.32	14.0	6.0	−20.0	***
11	I had better not handle patients during a nuclear accident.	2.64	1.29	−17.0	19.0	−2.0	***
12	I worry about patients' safety during a nuclear accident.	4.48	1.08	38.0	−14.0	−24.0	***
13	I will visit on a priority basis during a nuclear accident, except for off-limits areas.	3.95	1.18	16.0	8.0	−24.0	***
17	I will act under the direction of the home-visit nursing station during a nuclear accident.	3.29	1.53	3.0	6.0	−9.0	n.s
23	I will provide patients' information about related organizations when required.	3.24	1.5	1.0	8.0	−9.0	n.s

chi-square test, n=84, ***; $p<0.001$

Factors affecting the attitude to radiation emergency medicine:
Development of a Radiation Image Scale and assessment of factors affecting the image of radiation

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Abstract The purpose of this study was to develop a radiation image scale and examine its validity and reliability. In addition, factors affecting the image of radiation were examined. The subjects of the study were 218 nursing students and 173 nurses. These subjects completed a questionnaire containing 50 sets of adjective pairs relating to the image of radiation. Three factors were identified during the factor analysis (promax rotation using principal factor analysis). This scale was composed of 17 items classified using 3 factors: affectivity, usefulness, and certainty. Cronbach's alpha coefficient was 0.68 for the entire reliability of the scale. The alpha coefficient was 0.78 to 0.89 for each factor. Therefore, the validity and reliability of the scale was established to a certain degree. The factors affecting the radiation image using this scale were also examined. The results showed that the following people had a comparatively positive image of radiation in terms of affectivity: nurses as compared with the students in the nursing university; other persons who are familiar with radiographic examinations and radiation therapy; nurses who work for the special radiotherapy hospital as compared with the nurses who work for the general hospitals; and third-year students in the nursing university as compared with first-year students. The results suggest that the image of radiation in terms of affectivity may change through the accumulation of knowledge and skills and when there are increased opportunities to observe or conduct radiographic examinations and radiation therapy.

Key Words: radiation image, scale, radiation emergency medicine

INTRODUCTION

Attitudes toward radiation emergency medicine affect the practice of nursing. In the study described in this paper, we developed a tool for measuring an individual's image of radiation in order to obtain ideas that may prove useful in determining the direction that should be taken with regard to education on radiation emergency medicine on the basis that people's images of radiation affect their attitudes to radiation emergency medicine.

METHODS

Subjects and procedure

The subjects of this study were 218 students in a nursing university, 123 nurses who work for general hospitals, and 50 nurses who work in a special radiotherapy hospital. These subjects completed a questionnaire containing 50 sets of adjective pairs (radiation image scale) and their background information. For each adjective pair, we had the subjects give a grade of 1 to 7 to express which of the two adjectives they felt best

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described their image of radiation and to what extent they felt this adjective applied (a grade of 4 indicates that they felt that neither adjective applied).

Items listed on the radiation image scale

The method we employed to select the adjective pairs was as follows. In order to extract a variety of suitable adjectives to measure an individual's image of radiation, we showed 250 nursing students 10 stimulus words related to radiation. The subjects were asked to select up to 3 words that came to mind for each of the stimulus words. Following discussions among several researchers, we decided to use the following stimulus words: "Radiation," "Radioactive Exposure," "Radioactivity," "Radiotherapy," "X-ray Examination," "Nuclear Power Generation," "Chernobyl," "Atomic Bomb," "Nondestructive Tests Using Radiation," and "Cosmic Radiation." We obtained these 260 words from the responses of 202 nursing students. First, we selected adjectives that had been chosen on the following basis: they had a high frequency, were common to many stimulus words, were suitable as adjectives, and had been extracted in previous studies of people's images of radiation. Next, we identified 50 pairs of opposing adjectives amongst those that were selected. If an antonym of a selected adjective could not be found among the adjectives selected, we added an antonym with only a single meaning to form a pair. Thus, we selected 50 sets of adjective pairs relating to the image of radiation.

Data analysis

The coefficient of reliability (Cronbach's alpha) was calculated to examine the reliability of the scale, and its validity was verified by factor analysis employing promax rotation using the principal factor method. To assess statistical significance, the two-sample t-test and one-way analysis of variance were conducted by using SPSS Ver. 11.5 for Windows. Statistical significance was assumed for p-values less than .05.

RESULTS

We collected completed questionnaires from 338 participants (a recovery rate of 86.5%). There were 304 valid responses to the questionnaire. The participants in the survey were 189 nursing students and 115 practicing nurses (88 employed at general hospitals and 27 employed at a special radiotherapy hospital).

Development and extraction of factors from the radiation image scale

Two items were excluded from the radiation image scale in order to eliminate the ceiling effect and floor effect. Using the remaining 48 items, we conducted factor analysis using principal factor analysis and promax rotation. The factors were extracted with an eigenvalue of greater than or equal to 1.0. Then, using items with a factor loading of greater than or equal to 0.5 only for the extracted factors, we created a radiation image scale composed of 17 items classified using 3 factors.

The first factor comprised 9 items ("Destructive- Creative," "Distressing- Not distressing," "Worrying- Not worrying," "Fearful- Not fearful," "Harmful- Harmless," "Dangerous- Safe," "Uncomfortable- Comfortable," "Dark- Light," and "Strong- Weak"). Based on our belief that such terms reflect a positive or negative feeling toward the subject, we named this category "Affectivity." The second factor comprised 5 items ("Effective- Ineffective," "Necessary- Unnecessary," "Useful- Useless," "Usable- Unusable," and "Convenient- Inconvenient"). Based on our belief that such terms reflect a positive or negative evaluation regarding the use of the subject, we named this category "Usefulness." The third factor comprised 3 items ("Reliable- Unreliable," "Good- Bad," and "Controllable- Uncontrollable"). Based on our belief that such terms reflect a positive or negative evaluation regarding the subject's stability and reliability, we named this category "Certainty." The correlation coefficients between each factor were 0.21 to 0.52. Cronbach's alpha coefficient was 0.68 for the entire reliability of the scale. The alpha coefficient was 0.78 to 0.89 for each factor.

Correlation between background information and image of radiation

Factors affecting the radiation image using this scale were also examined. These results show that the image the participants have of radiation tended to be negative for all items in the "Affectivity" category, but positive for all items in the "Usefulness" and "Certainty" categories.

The following people had a comparatively positive image of radiation in terms of affectivity: nurses as compared with nursing students; those familiar with radiographic examinations and radiation therapy; nurses working at a special radiotherapy hospital; those who have attended lectures on radiation-related matters or on radiographic examinations and radiation therapy; those who have experience working on a radiation-related ward; third-year nursing students as compared with first- or second-year nursing students; and nursing students with experience caring for patients who have undergone a radiographic examination and radiation therapy as part of their nursing practice. Similarly, the following people had a positive image of radiation in terms of the usefulness of radiological applications: nurses as compared with nursing students; nurses working at a special radiotherapy hospital; and nursing students with experience caring for patients who have undergone a radiographic examination and radiation therapy. In addition, the following felt that radiation is something that people can control: nurses as compared with nursing students; nurses working at a special radiotherapy hospital; those who have attended lectures on radiation-related matters or on radiographic examinations and radiation therapy; and those who have worked on a radiation related ward.

DISCUSSION

Scale development and extraction of factors

Since Cronbach's alpha coefficient was 0.68 for the entire reliability of the scale, it can be concluded that this scale largely maintained a certain degree of internal consistency. The alpha coefficient was 0.78 to 0.89 for each of the subordinate scales, so the internal consistency of the scale was maintained. Based on the preliminary survey of nursing students and previous studies, adjective pairs used to form the basis of the scale were selected through consultations with several researchers. Therefore, we consider the validity of the content of this scale to have been ensured. In addition, since the factor structure was defined by factor analysis, we consider construct validity to have been ensured.

Factors affecting the image of radiation

The participants' image of radiation tended to be negative for all items in the "Affectivity" category, while their image of radiation tended to be positive for all items in the "Usefulness" and "Certainty" categories. In other words, the participants tended to have a negative attitude toward radiation overall, but felt that radiological applications were useful, that radiation is reliable, and that control could be exercised over radiation.

The results of this study suggest that those who become familiar with radiation through their work or have many opportunities to learn about radiation lose their negative attitude toward radiation and start to view it as useful and controllable. The results of the factor analysis revealed that the negative correlation between certainty and affectivity is high. If a phenomenon is rationally interpreted as a result of the acquisition of knowledge, the image of its usefulness and certainty can be corrected. The results of our study suggest that developing a positive image of radiation's certainty may be connected to changing an individual's negative affectivity to radiation. However, once someone's attitude toward radiation risk is fixed, it is not easy to change it. Therefore, to change people's negative image of radiation, we believe that continued education and accumulation of knowledge is more effective than one-time education courses.

Suggestions for education regarding radiation emergency medicine

Joy, anger, humor, pathos, likes, dislikes, and other such emotions influence a subject's attitude toward an object or a situation and the value they attach to it. If nurses have a negative image of radiation (especially in terms of their affectivity), they may be reluctant to perform patient care in radiation emergency medicine. We believe that the validity and reliability of the developed radiation image scale was established to a certain degree, and that it is a useful scale since only 17 questions are asked. It is our belief that using this scale to ascertain changes in a subject's image of radiation will prove useful as part of an evaluation of education on radiation and radiation emergency medicine.

ACKNOWLEDGMENTS

This study was supported by a Grant for Co-medical Education Program in Radiation Emergency Medicine by the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Study on risk communication in education of radiation protection: Risk perception in health sciences students

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Abstract. The aim of this study was to clarify the perceptions of the students in health sciences school on radiation risk and protection. The subjects were first-grade students of health sciences school. A questionnaire survey was conducted in 201 students majoring in nursing (N), medical technology (T), physical therapy (PT), occupational therapy (OT) and radiological technology(R) in Hirosaki University. The risk from common radiation, such as natural radiation or chest X-rays, was perceived as being significantly riskier by the N students than the R students. In addition, the risk of natural radiation, radium and airport X-ray on score were significantly felt more scared by the students who did not select the physics than those selected the physics in high school. N students also had greater fear of radiation than R students.It is concluded that the differences of risk perception on radiation and educational background on radiation might be caused by education contents.

Key words: risk perception on radiation, risk communication, education, radiation protection, health sciences students

1. Introduction

The concern and receptibility of the medical radiation in the public is comparatively high, because the benefit of the medical exposure is generally clear[1)]. But Gonzrez reported there a lot of people who felt the anxiety on the influence or the risk of the radiation exposure for radiation diagnosis[2)]. In addition, many medical staffs also engaged in the medical care with feeling the anxiety of radiation exposure[3)]. Fear of radiation is highly communicable, and can negatively affect patient care[4)]. Therefore, a systematic radiational education is required for improving an unnecessary anxiety[4) 5)]. Further, the medical staffs play an important role on the risk communications in sympathizing the patient's anxiety on radiation and dealing with it adequately. However, there are few opportunities for students excluding medical and radiological technology courses to receive systematic education on radiation protection in the medical and health sciences schools[6)]. The aim of this study was to clarify the perceptions of the students in health sciences school on radiation risk and protection.

2. Methods

2-1 Subjects

The subjects were first-grade students of health sciences

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school. A questionnaire survey was conducted in 161 students majoring in nursing (N), medical technology (T), physical therapy (PT), and occupational therapy (OT) (43 males, 118 females), and 40 students majoring in radiological technology (following R; 29 males, 11 females).

Table.1. Contents of ' Introduction of Basic Radiation

1	Pioneer of radiology
2	Radiation and Radioactivity
3	Detection of Radiation
4	Radiation exposure's modality and Influence on human body (1)
5	Radiation exposure's modality and Influence on human body (2)
6	Mechanism of nuclear plant and nuclear reprocessing, Security Precaution
7	Outline of Radiation Emergency Medicine
8	Test

2-2 Education on radiation

Students majoring in N, T, PT and OT took the course concerning the basic radiation protection in the April-June; 'Introduction of Basic Radiation' (8 times / [90 minutes / time])(table.1). Contents of the course were wide and shallow. Students of R didn't take the course about radiation protection.

2-3 Methods

Data collection and analysis were conducted between June and July in 2010. Students majoring in N, T, PT and OT were measured after the final lecture in 'Introduction of Basic Radiation'. The survey consisted of questions associated with radiation itself and 10 kinds of questions on "risk of damage to one's health by radiation or radioactive substances" (health risk of radiation), which were evaluated by 11-point scale respectively. The items of survey referred to the study of Kanda[7]. Then, we measured 4 questions consisted of risk perception and factor influencing risk perception (Table.2.).

Table.2. Question item of risk perception and the factor influencing risk perception

1	How do you fear the radiation?
2	How difficult is the knowledge of radiation?
3	How much influence on the human body of the radiation do you know?
4	How much are you interested about the radiation?

2-4 Statistics Analysis

We compared the answers among the students with each major. The analysis was done using one-way analysis of variance and Bonferroni test for multiple comparisons.

3. Results

The subjects were 193. Backgrounds of the subjects were shown in Table3. A lot of N students had selected the chemistry and the

Table.3. Background of the subjects

	Total	sex*1		Elective Subjects of Science in high school				Nuclear power plant
		Male	Female	Physics*2	Chemistry	Biology*3	Physical Geography	
Nursing (N)	70	11	64	22	72	56	0	56
Medical Technology (T)	34	15	24	18	36	23	0	28
Physical Therapy (PT)	20	8	11	12	17	10	1	16
Occupational Therapy (OT)	20	8	12	9	17	13	0	11
Ragiological Technology (R)	35	29	11	38	39	5	0	11
Total	193	71	122	99	181	107	1	11

Subjects data were 193 at all. The values are the numbers of people.
Nuclear power plant are the numbers of people that were born and raised in the prefecture where the nuclear plant exists.
Statistical Analysis was used by Chi-square test, and statistical significance was defined as $p<0.05$.
*1 The rate of sex were statistically significant differences between N and R ($p<0.001$).
*2 The rate of students selected the physics were significant differences between (N) and (R) ($p<0.001$).
*3 The rate of students selected the biology were significant differences between (N) and (R) ($p<0.001$).

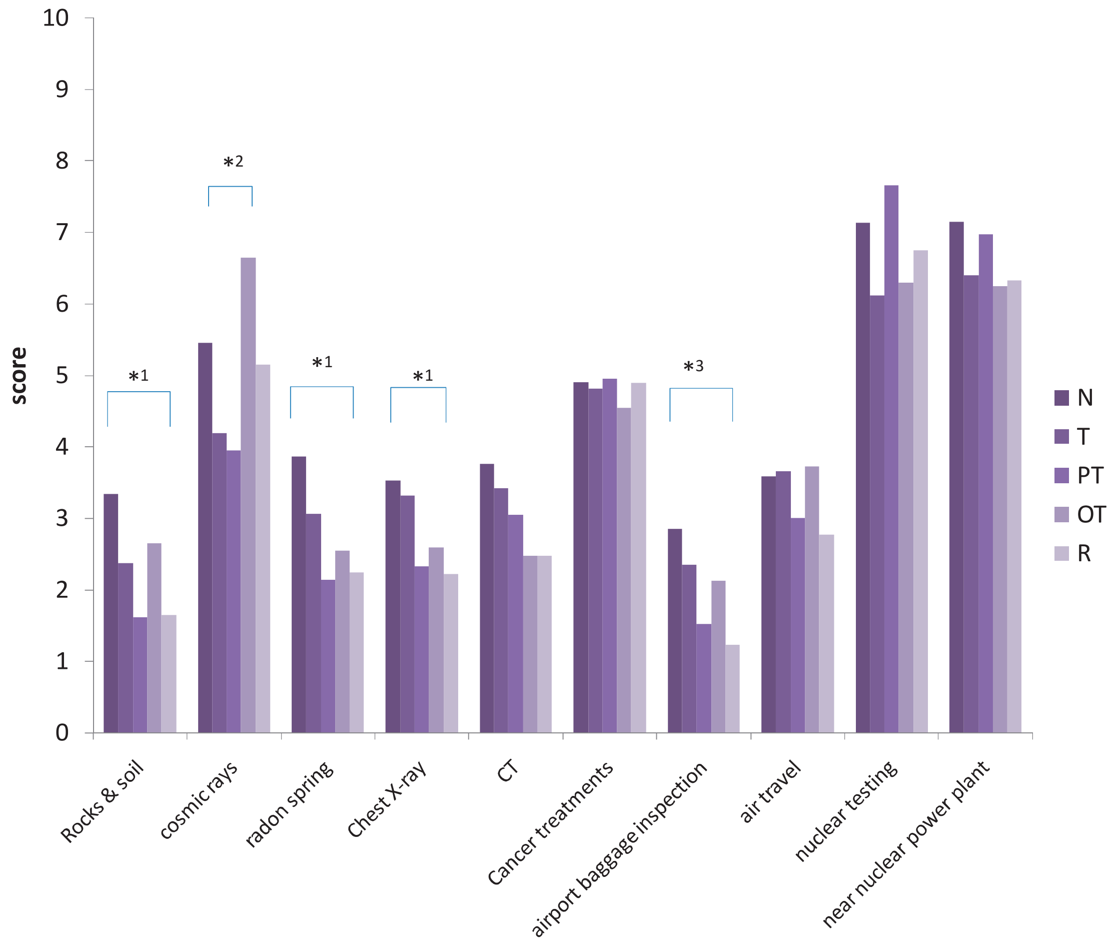

Figure.1. Risk of damage to one's health by radiation or radioactive substances

Statistical analysis: one-way ANOVA and Bonferroni test for multiple comparison
*1 :$p<0.05$, for comparison between N and R
*2 :$p<0.05$, for comparison between T and OT,PT and OT
*3 :$p<0.01$, for comparison between N and R

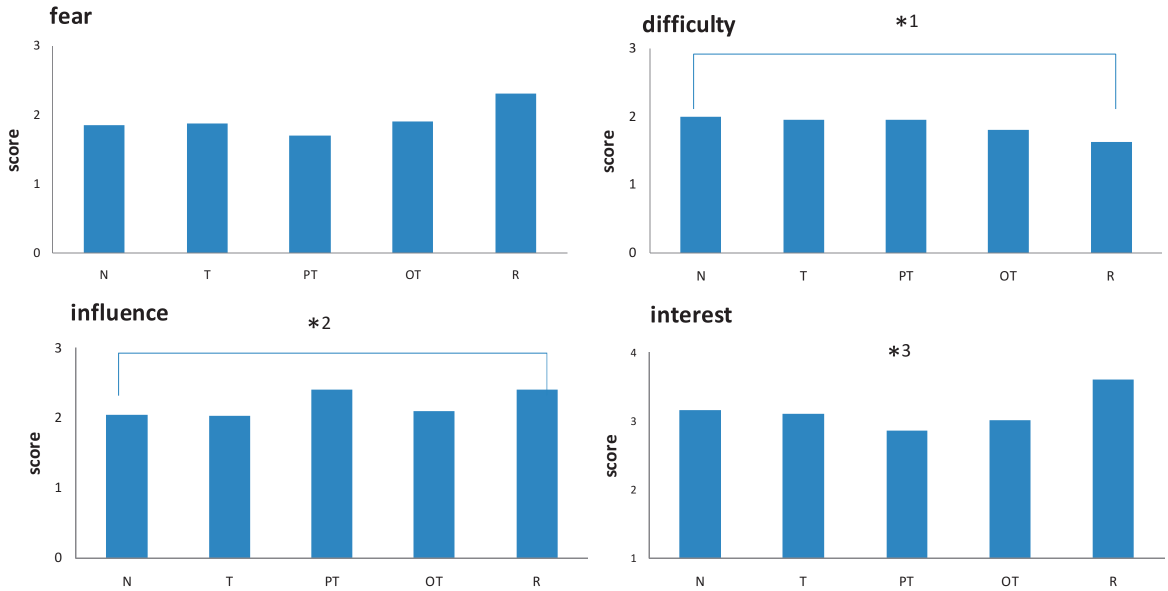

Figure.2. Risk perception and the factor influencing on risk

Statistical analysis: one-way ANOVA and Bonferroni test for multiple comparison
*1 :p<0.05, for comparison between N and R
*2 :p<0.05, for comparison between N and R, N and PT
*3 :p<0.01, for comparison between N and others courses

biology in high school, although all R students had selected the physics and the chemistry. With regard to the health risk of radiation, the risk from common radiation, such as natural radiation or chest X-rays, was perceived as being significantly riskier by the N students than the R students. And the risk from common radiation, such as cosmic radiation was perceived as being significantly riskier by the OT students than the MT and PT students (Fig.1.) In addition, the risk of natural radiation, radium and airport X-ray on score were significantly felt more scarier by the students did not select the physics than those selected the physics($p<0.05$). There were no significant differences among selecting the chemistry and the biology, nuclear power plant. N students also had greater fear of radiation than R students. N and MT students were felt more difficult about the radiation than R. R students had significantly more interest in radiation than other students (Fig.2.).

4. Discussion

Nursing students think that radiation is fearful compared with radiological technology students. A life science students have high risk perception compared with an engineering students[8). As compared with radiological students, nursing students are close to the life science more. According to the report of Japan Atomic Energy Relations Organization[9)], 50% of the civilian did not know about natural radiation, and they thought the radiation to have been made by the contemporary science. It seemed that the students who were not taking physics such as nursing students did not know about a basic radiation like a natural radiation just like the results of civilians.

Risk perception of having been once fixed to them does not change simply. Even if fearful, it is thought that unnecessary uneasiness can be wiped away by advancing educational contents which increase management possibility. Since radiological students have entered the radiation course with interest, it is guessed that the interest about radiation was higher.

5. Conclusion

It is concluded that the differences of risk perception on radiation and educational background on radiation might be caused by education contents and we should examine an educational content further.

6. Acknowledgements

This study was supported by a Grant for Co-medical Education Program in Radiation Emergency Medicine by the Ministry of Education, Culture, Sports, Science and Technology, Japan. The author thanks Dr. Hideaki Yamabe for editorial assistance.

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Relationship between radiosensitivity and Nrf2 target gene expression in human hematopoietic stem cells

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Abstract. NFE2-related factor 2 (Nrf2), which belongs to the cap ‘‘n’’ collar family of basic region leucine zipper transcription factors, is a key protein in the coordinated transcriptional induction of expression of various antioxidant genes. The purpose of this study was to analyze the expression of Nrf2 target genes, such as heme oxygenase 1 (HO-1), ferritin heavy polypeptide 1 (FTH1), NAD(P)H dehydrogenase, quinone 1 (NQO1), glutamatecysteine ligase catalytic subunit, glutamate-cysteine ligase modifier subunit, glutathione reductase (GSR) and thioredoxin reductase 1 (TXNRD1), after X irradiation of $CD34^+$ cells that were prepared from human placental/umbilical cord blood hematopoietic stem cells (HSCs). We evaluated the relationship between radiosensitivity and expression of Nrf2 target genes in HSCs. The number of colony-forming cells derived from 2-Gy irradiated HSCs decreased to approximately 20% of the non-irradiated control. At the same time, the mRNA expression of HO-1, FTH1, NQO1, GSR and TXNRD1 was significantly increased after X irradiation. A statistically significant negative correlation was observed between the surviving fraction of HSCs and the intrinsic NQO1 mRNA expression, indicating that HSCs in which NQO1 mRNA levels are low may also be radioresistant. The present results suggest that the antioxidant system associated with Nrf2 is involved in the radiosensitivity of HSCs.

Key Words: reactive oxygen species Nrf2, hematopoietic stem cells, radiosensitivity

Introduction

Low-LET ionizing radiations, such as X rays and γ rays, generate reactive oxygen species (ROS) that cause biological damage and change cellular signaling, with the effects dependent on their concentration at a given time (1,2). Several enzymatic and non-enzymatic antioxidants play an important role in eliminating either ‘‘intracellular’’ or ‘‘intercellular’’ ROS. NFE2-related factor 2 (Nrf2) is a key protein in the coordinated transcriptional induction of expression of various antioxidant genes. Nrf2, which belongs to the cap ‘‘n’’ collar family of basic region leucine zipper transcription factors, undergoes a rapid translocation into the nucleus in response to various inducers such as electrophiles and ROS (3-5). After translocation into the nucleus, Nrf2 recognizes and binds to antioxidant response elements in the promoter regions of its target genes. Hematopoietic stem cells (HSCs) can self-renew and differentiate into all hematopoietic lineages throughout the lifetime of an organism. HSCs are sensitive to extracellular oxidative stress such as radiation and chemotherapeutic agents (6-11). Furthermore, their radiosensitivity varies among individuals (12, 13). Therefore, the response of gene expression to ionizing radiation may depend on individual differences in the radiosensitivity of hematopoietic stem/progenitor cells (HSPCs). However, the relationship between radiosensitivity and Nrf2 target genes in HSCs has not yet been studied. The purposes of this study were to analyze the expression of the Nrf2 target genes heme oxygenase 1 (HO-1), ferritin heavy polypeptide 1 (FTH1), NAD(P)H dehydrogenase, quinone 1 (NQO1), the glutamate-cysteine ligase catalytic subunit (GCLC), the glutamate-cysteine ligase modifier subunit (GCLM), glutathione reductase (GSR), and thioredoxin reductase 1 (TXNRD1) after X irradiation of $CD34^+$ cells prepared from human placental/umbilical cord blood (CB) HSCs and to evaluate the relationship between radiosensitivity and expression of Nrf2 target genes in these cells.

Results and Discussion

This study was approved by the Committee of Medical Ethics of Hirosaki University Graduate School of Medicine. HSPCs were enriched from human CB using the $CD34^+$ cell sorting kit. To assess the radiosensitivity of each HSC (n = 10), the distribution of each progenitor cell, including CFU-GM, BFU-E and CFU-Mix, was evaluated in both unirradiated and irradiated cells. As a result of the 2-Gy irradiation, each progenitor-derived colony formation decreased. The average surviving fraction of CFCs was 0.22 ± 0.046. The mRNA expression of HO-1, FTH1, NQO1, GSR, TXNRD1, GCLC and GCLM was analyzed 6 h after X irradiation. We found that the mRNA expression levels of HO-1, FTH1, NQO1, GSR and TXNRD1 increased significantly after X irradiation (Fig. 1). Because excessive iron induces injury to cells via ROS generation, iron homeostasis regulated by HO-1 and FTH1 plays an important role in protection against oxidative stress (14-16). No significant difference was observed in GCLC and GCLM, even though these two genes have a critical role in redox environment homeostasis. GCLC and GCLM are the first rate-limiting enzymes, and their activities depend on various types of electrophiles (17, 18), suggesting that ROS generated by X radiation may not be involved in the induction of GCLC and GCLM. Nonirradiated HSCs also greatly increased Nrf2 target gene expression (Fig. 1).

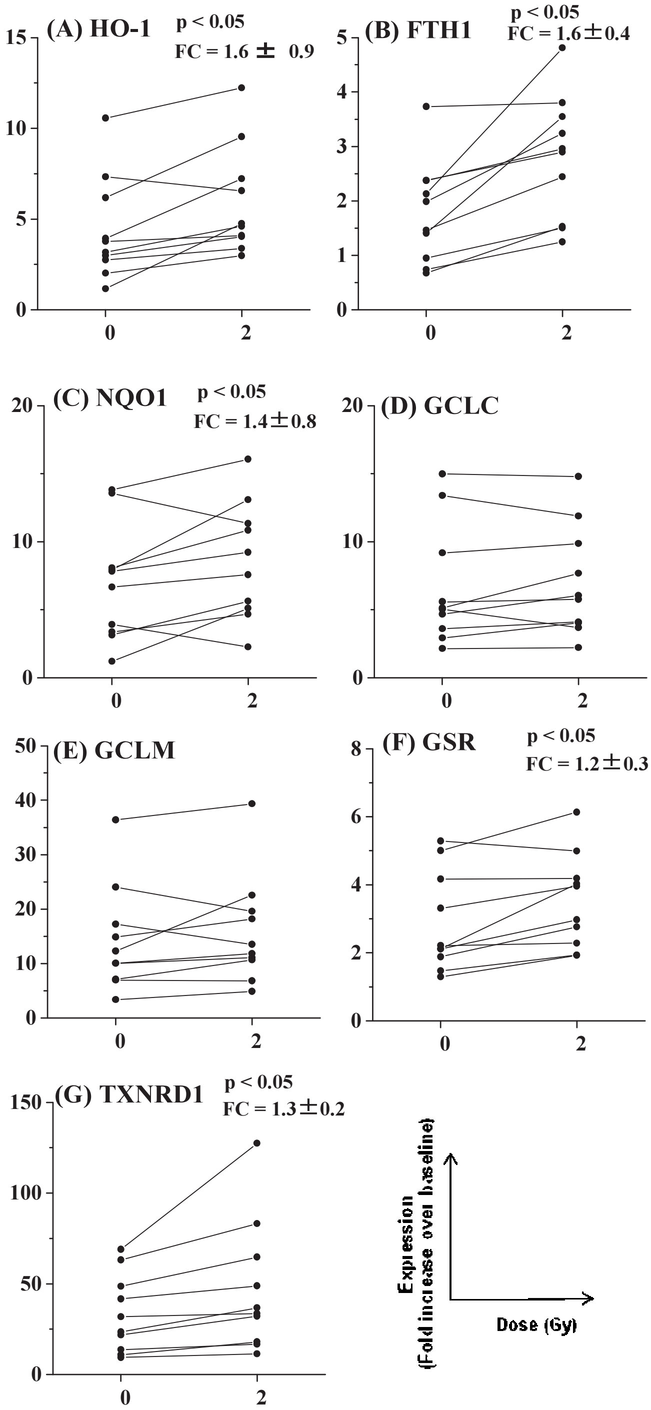

Fig. 1. Nrf2 target gene expression of HSCs after X irradiation

The oxygen concentration in the peripheral blood of a fetus is generally lower than that in an adult, and thus HSCs prepared from CB suffer oxidative stress when cultured in a humidified atmosphere (19). In this study, the Nrf2 system might also be up-regulated by oxidative stress generated during culture. However, Nrf2 target gene expression of X-irradiated HSCs is higher than that of nonirradiated HSCs; thus exposure to X rays clearly induced expression of genes in the Nrf2 system.

A few reports have described an increase in Nrf2 target gene expression after ionizing radiation exposure in mice and rats (20-22). However, these reports have evaluated only the responses of organs such as the liver and pancreas after whole-body irradiation. Our results are the first to show that the Nrf2 system in highly radiosensitive cells such as HSCs is induced by X rays as a result of oxidative stress. We propose that the induction of Nrf2 by X irradiation of HSCs arises through one of two pathways: Nrf2 is induced directly by ROS, or Nrf2 is induced indirectly as a result of the activation of ataxia telangiectasia mutated (ATM) via DNA damage. Although Li et al. suggested that ATM controls Nrf2 via protein kinase C delta and contributes to the antioxidant enzyme expression (23), we assume that either Nrf2 is induced directly by ROS or Nrf2 is induced indirectly as a result of the activation of ATM via DNA damage.

Previous studies reported a relationship between radiosensitivity and Nrf2 target gene expression. Radiation-resistant mice exhibit higher antioxidant enzyme activities than radiation-sensitive mice (24). In addition, the induction of HO-1 by cobalt protoporphyrin IX, which induces HO-1 expression, inhibits radiation induced apoptosis in mouse endothelial cell lines (25). Furthermore, the radiosensitivity of HSCs in steadystate human peripheral blood varies among individuals (Fig. 1) (13). Therefore, we hypothesized that Nrf2-regulated gene expression might be involved in the individual radiosensitivity of HSCs. A statistically significant negative correlation was seen between the surviving fraction of CFCs and NQO1 mRNA expression (Fig. 2).

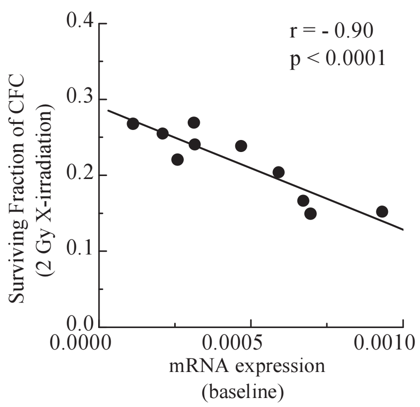

Fig. 2 Relationship between the CFC surviving fraction and Nrf2 target gene (NQO1) expression.

Myeloid cells of NQO1 knockout mice are resistant to radiation-induced apoptosis (26). Therefore, the present results suggest the possibility that a cell with high NQO1 mRNA levels is radioresistant compared to a cell with low levels. In addition, the population of $CD34^+/CD38^-$ cells contains more immature HSPCs than the population of $CD34^+/CD38^+$ cells (27, 28). Hayashi et al. demonstrated that the $CD34^+/CD38^-$ stem cell population prepared from CB is sensitive to radiation-induced apoptosis as well as to the production of intracellular O^{2-} compared to the more differentiated $CD34^+/CD38^+$ and $CD34^-/CD38^+$ cells (29). Therefore, a difference in the population of $CD34^+/CD38^+$ and $CD34^+/CD38^-$ cells included in individual HSC populations may be able to influence individual radiosensitivity significantly. In the present study, however, most of the HSCs were $CD34^+/CD38^+$, and the $CD34^+/CD38^-$ cell population was as low as about 3% in each individual. No significant relationship was observed between the surviving fraction of HSCs and the ratio of $CD34^+/CD38^-$ cells to the HSC population. Although the individual expression of NQO1 influenced radiosensitivity, the results suggest that there were no individual differences among the HSC populations.

This study was performed under restricted conditions, such as a irradiation with 2 Gy and a 6-h time limit, because the number of $CD34^+$ cells obtained from one CB sample was very small. In planning this study, there were two reasons to select a dose of 2 Gy. First, the standard dose of radiation for cancer radiotherapy is 2 Gy per fraction. Second, a CFU-Mix multilineage colony is not detected frequently above 2 Gy. Analysis was performed 6 h after X irradiation because some reports have indicated that HO-1 mRNA expression was maximum at about 6 h after X irradiation and lipopolysaccharide stimulation (20, 30). To investigate the other issues mentioned previously, larger numbers of cells will be needed. In addition, it will be necessary to perform further experiments to analyze the nuclear translocation of Nrf2, the relationship between the radiosensitivity and Nrf2 system in more classified HSCs, and the NQO1 function for radiosensitivity.

Acknowledgments

We are grateful to the mothers and babies who supplied us the placental/umbilical cord blood and to the medical staff at Hirosaki National Hospital for collecting the samples. This study was supported by KAKENHI Grants-in-Aid for the promotion of Science and Young Scientist (Nos.

18790863 and 20790874 KT), Scientific Research (B) (Nos. 18390327 and 21390336 IK) and by a Grant for Co-medical Education Program in Radiation Emergency Medicine by the Ministry of Education, Culture, Sports, Science and Technology, Japan. This work was also supported by a Grant for Hirosaki University Institutional Research (2008, 2009).

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Maturation stimuli-dependent differential induction from X-irradiated human monocytes to dendritic cells

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Abstract Dendritic cells (DCs) play an essential role in the immune system. However, little is known whether the DCs generation is affected after radiotherapy. We have recently reported that X-irradiated monocytes can differentiate into DCs and then mature after TNF-α stimulation in terms of phenotypic characteristics, while their several functions such as the matrix metalloproteinase-9 (MMP-9) activity are impaired in comparison to controls (Yoshino et al., J. Radiat. Res., 49, 2008). DCs respond to various types of maturation stimuli, including proinflammatory cytokines and pathogen-derived components. Therefore, the present study investigated whether X-irradiation of monocytes influenced the maturation of DCs in response to specific maturation stimuli. The use of human buffy coats was approved by the Committee of Medical Ethics of Hirosaki University Graduate School of Medicine. Monocytes were separated from the buffy coat and exposed to X-rays at 2, 5 and 10 Gy. To prepare immature DCs (iDCs), irradiated monocytes were cultured in the presence of rhGM-CSF and rhIL-4. To prepare mature DCs (mDCs), iDCs were stimulated by lipopolysaccharide (LPS) or a stimulus mixture (MIX). The phenotype of the DCs was analyzed by flow cytometry and the MMP-9 activity was assayed by gelatin zymography. When iDCs were stimulated by LPS, the expression level of the CD80 and DCs' maturation marker CD83 on the DCs from X-irradiated monocytes was lower than that of non-irradiation. However, no decrease was observed in the MIX stimulation. When iDCs were stimulated by LPS, the MMP-9 activity in the culture supernatants was impaired in the DCs from the X-irradiated monocytes in comparison to non-irradiation. However, in the case of MIX stimulation, MMP-9 activity in the culture supernatants of DCs from X-irradiated monocytes was largely maintained in comparison to non-irradiation. These results suggest that the influence of X-irradiation on monocytes in the maturation of DCs depends on the type of maturation stimulus.

Key Words: dendritic cells, maturation, X-ray irradiation

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Introduction

Dendritic cells (DCs) are a type of antigen-presenting cell which plays an essential role in the immune system.[1)] Recent immunotherapeutic research has been focused on the use of DCs as potential cellular vaccines against malignant tumors. However, little is known whether the DCs generation is affected after chemotherapy and radiotherapy. Especially, the influence of ionizing radiation remains to be elucidated. Therefore, we have focused our attention on human peripheral blood monocytes, which are known to be the DC precursors of myeloid DCs, and reported that X-irradiated monocytes can differentiate into DCs and then mature after TNF-α stimulation in terms of phenotypic character, while their several functions such as the matrix metalloproteinase-9 (MMP-9) activity and the ability to stimulate allogeneic T cells are impaired in comparison to controls.[2)]

Recent reports propose a various type of maturation stimulus including proinflammatory cytokines and pathogen-derived components on processing DCs for immunotherapies. Therefore, the present study investigated whether the influences of X-irradiation to monocytes on the maturation of DCs depend on the type of maturation stimulus.

Results

X-irradiation impairs the response of DCs to lipopolysaccharide (LPS) in terms of cell surface antigens expression

The use of human buffy coats was approved by the Committee of Medical Ethics of Hirosaki University Graduate School of Medicine. DCs were generated from monocytes according to previously published protocols [3)] with some modification. In brief, to prepare the immature DCs (iDCs), monocytes were cultured in the presence of rhGM-CSF plus rhIL-4. Each iDC was stimulated by LPS or a cytokine mixture (rhTNF-α, rhIL-1β, rhIL-6, and PGE_2: MIX) for 48 hr, and then phenotypic characteristics of DCs were analyzed by flow cytometry. In LPS stimulation, the expression level of the co-stimulatory molecule CD80 and DCs' maturation marker CD83 on the DCs from X-irradiated monocytes was lower than that of the DCs from non-irradiated monocytes (Fig 1). However, no decrease was observed in the DCs stimulated by MIX (Fig. 1).

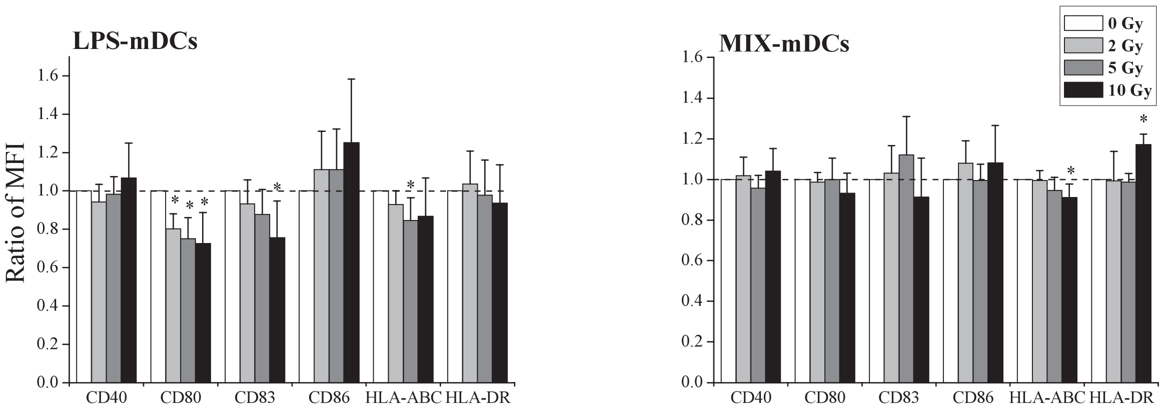

Figure 1. Cell surface antigens expression on DCs stimulated by LPS or MIX. The ratio of mean fluorescence intensity (MFI) for each cell surface antigen are expressed as the mean + SD of from four to seven different individuals.
* indicates $p<0.05$ by two-sided Mann-Whitney's U-test.

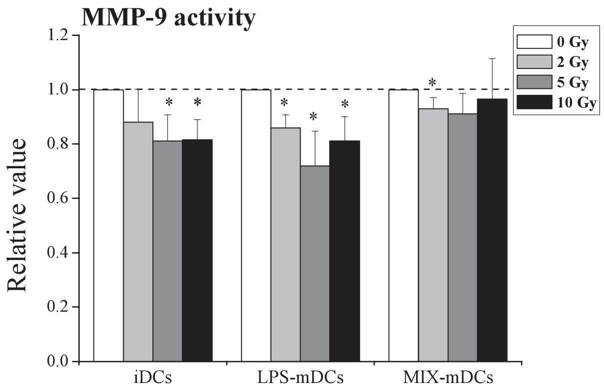

Figure 2. Total MMP-9 activity of iDCs or DCs stimulated by LPS or MIX. The data of iDCs indicate the mean + SD of five different individuals. The data of LPS- or MIX-mDCs indicate the mean + SD of four different individuals.
* indicates $p<0.05$ by two-sided Mann-Whitney's *U*-test.

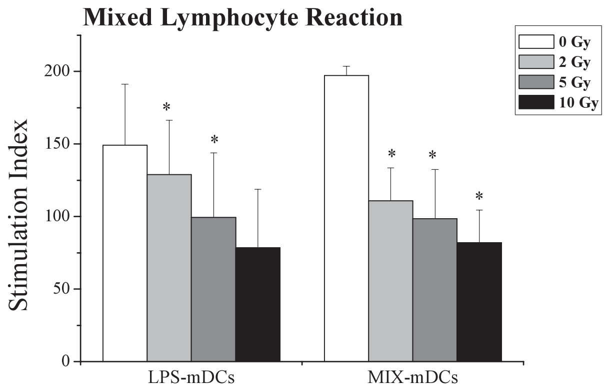

Figure 3. Stimulating ability of DCs on allogeneic T cell proliferation. Each mDC was 20 Gy-irradiated, and then were co-cultured with allogeneic T cells. T cells proliferation was determined by the incorporation of [^{3}H]-thymidine. The results are shown as stimulation index which is the ratio of cpm in the presence of DCs to cpm of only T cells. Data are three different individuals.
* indicates $p<0.05$ by two-sided paired *t*-test.

X-irradiation impairs the response of DCs to LPS in terms of total matrix MMP-9 activation

The total MMP-9, which is important factor for DCs' migration, contained in the culture supernatant of each DC was analyzed by substrate zymography according to previous report.1) The total MMP-9 activity of iDC and LPS-mDCs was lower in the DCs from X-irradiated monocytes compared with DCs from non-irradiated monocytes (Fig. 2). However, no large decrease in the MMP-9 activation was observed in MIX stimulation.

X-irradiation impairs the allostimulatory ability of DC irrespective maturation stimuli

mDCs can stimulate proliferation of allogeneic leukocytes and this ability is often used as a surrogate marker of their activation. Therefore the ability of DCs to stimulate allogeneic T cells was examined. Irrespective of types of maturation stimuli, the ability of DCs to stimulate allogeneic T cells proliferation was lower in DCs from X-irradiated monocytes compared with DCs from non-irradiated control (Fig. 3).

X-irradiation does not affect the expression of Toll-like receptor 4 (TLR4) on iDCs

To investigate the reasons of low response to LPS after X-irradiation, the expression of TLR4 on iDCs, which is receptor for LPS, was analyzed by flow cytometry. Although iDCs expressed both surface and intracellular, there was no difference in TLR4 expression between non- and X-irradiation (Fig. 4). These results indicate that the low response of DCs from X-irradiated monocyte to LPS was independent of TLR4 expression.

X-irradiation changes the intracellular reactive oxygen species (ROS) levels induced by maturation stimuli

As the intracellular ROS is important for signal transduction, the intracellular ROS levels were analyzed. Irrespective of maturation stimuli, the ROS levels were lower in DCs from X-irradiated monocytes compared with non-irradiated control (Fig. 5). The ROS levels of DCs from X-irradiated monocytes were partially recovered at late time point in MIX stimulation, whereas those remained lower in LPS stimulation.

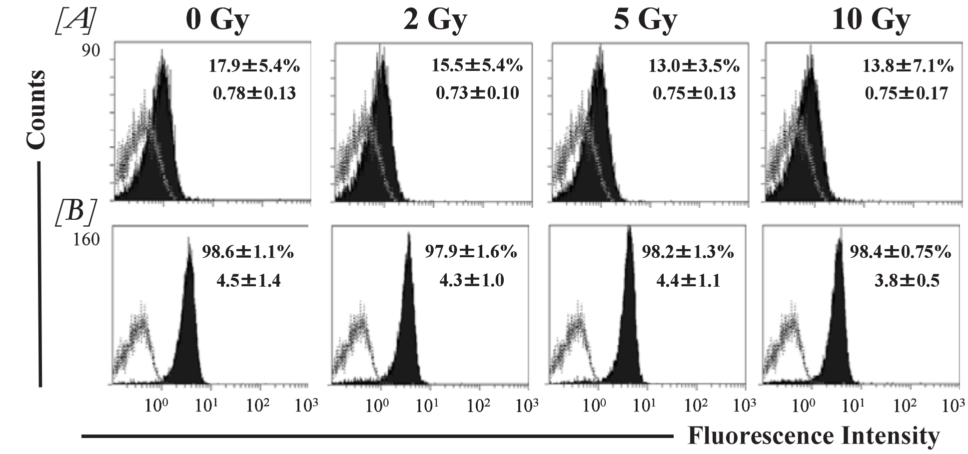

Figure 4. Cell surface and intracellular TLR4 expression of iDCs. The cell surface [A] or intracellular [B] TLR4 expression was analyzed flow cytometer. The data of histogram are one of four different individuals. Dotted line indicates isotype control. Inset number means positive percentage and MFI of TLR4. Data are mean ± SD of four different individuals.

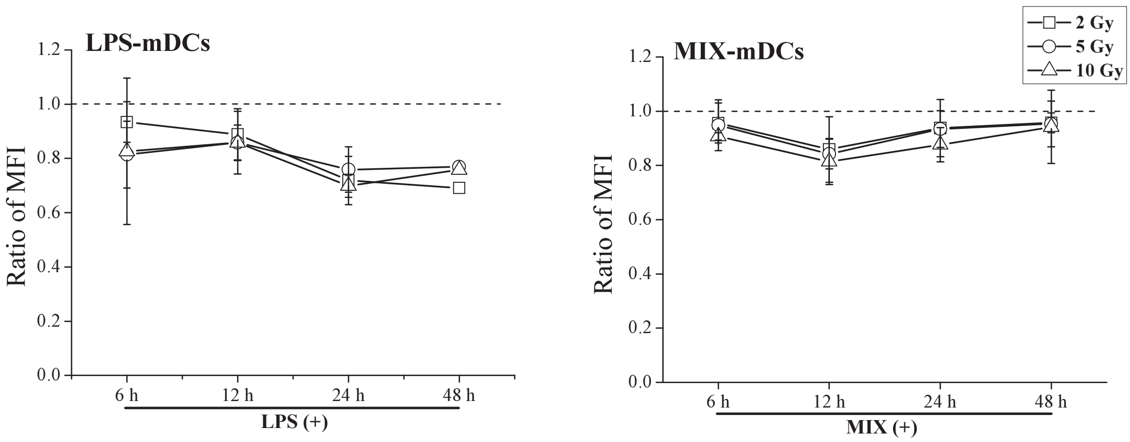

Figure 5. Kinetics of intracellular ROS levels after stimulation by LPS or MIX. The intracellular ROS levels in mDCs were analyzed using 2',7'-dichlorodihydrofluorescein diacetate (H_2-DCFDA). Ratio of MFI for H_2-DCFDA at each time point was obtained by calculating a relative value against non-irradiated control in each individual. Data are expressed as the mean ± SD of from one to three different individuals.

Conclusions

The present study indicates that the influences of X-irradiation to monocytes on the maturation of DCs depend on the type of maturation stimulus. Furthermore, DCs derived from X-irradiated monocytes show low response to LPS compared with non-irradiated control.

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Effect of ionizing radiation on differentiation of mouse induced pluripotent stem cells into the three germ layers

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Abstract. The present study aimed to investigate the effect of ionizing radiation on differentiation and proliferation of mouse induced pluripotent stem (iPS) cells. Compared with mouse hematopoietic stem/progenitor cells, iPS cells were less sensitive to radiation. To observe the effect of ionizing radiation on the early differentiation pathway of iPS cells, embryoid body (EB) formation was assessed. Although EB formation was observed at all radiation doses, EB diameter decreased in a radiation dose-dependent manner. At the same time, the differentiation-related specific gene expression detected in the initial iPS cells and EB cells was analyzed. The expression of the endoderm marker *Afp* increased remarkably in EB cells derived from nonirradiated iPS cells; however, in irradiated cells, this expression significantly decreased in a radiation dose-dependent manner. A significant decrease was observed in the expression of the pluripotent stem cell markers *Nanog* and *Oct-4* and the early mesoderm marker *Brachyury*. The present results suggest that there is a difference in radiosensitivity in the early differentiation pathway of iPS cells to the three germ layers, with the sensitivity being highest in the differentiation pathway to endoderm.

Key Words: iPS cells, early differentiation, irradiation

Introduction

Induced pluripotent stem cells so called iPS cells were first generated from mouse adult fibroblasts through reprogramming by transduction of four defined transcription factors (Oct3/4, Sox2, Klf4, and c-Myc) (1). Thereafter, human iPS cells were generated from human adult fibroblasts using the above-mentioned transcription factors (2). Many researchers are investigating the application of iPS cells in regenerative medicine, because iPS cells can differentiate into various types of functional cells (3-12). In general, immature cells are thought to be more radiosensitive compared with mature cells, except lymphocytes (13, 14). However, little is known regarding the influence of ionizing radiation on differentiation and proliferation of stem cells, especially iPS cells. In this study, we assessed the effect of ionizing radiation on the differentiation of mouse iPS cells into the three germ layers.

Material and Methods

The iPS cells used in this study were transferred from the RIKEN BioResource Center (15). iPS cells were irradiated at a dose of 1, 2, 4 or 7.5 Gy with X-rays using a dose rate of 3.3–3.4 Gy/min. The nonirradiated and irradiated iPS cells were cultured with methylcellulous culturing medium containing 10% FBS. The culture for EB formation was performed in a round-bottomed conical polypropylene tube. After 5 days of culture, EBs were measured a diameter of EB size. After 7 days of culture, each EB was harvested to extracte the total RNA. Gene expression was assessed by real-time RT-PCR performed using SYBR green technique.

Results and Discussion

In order to determine the radiosensitivity of iPS cells, we performed the clonogenic assay. The D_0 value of iPS cells and mouse lineage negative hematopoietic stem/progenitor cells (HSPCs) derived from bone marrow was 1.85 and 1.11, respectively. These results show that iPS cells are more resistant to radiation compared with HSPCs. These findings are contrary to a basic theory in which immature cells are more radiosensitive than mature cells. A previous study reported a similar radiation survival curve in the study of mouse ES cells (16). Therefore, when we consider the previous results and our's, the radiosensitivity of pluripotent stem cells would be low to some extent (Figure 1).

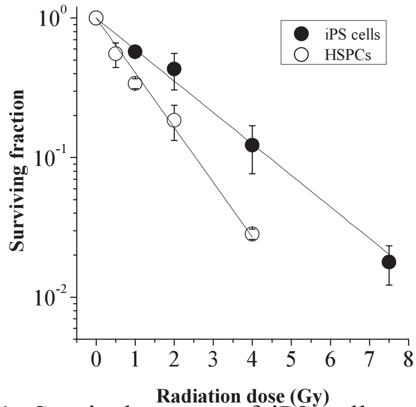

Figure 1. Survival curves of iPS cells and mouse HSPCs.

To see the differentiation potential of iPS cells, non-irradiated and irradiated iPS cells were assayed for EB formation. The plating efficiency of EB formation was 100% for nonirradiated iPS cells. Interestingly, EBs were formed 100% for the irradiated iPS cells up to 7.5 Gy. The colony morphology of EB resembled a highly dense mass as shown in this figure. The diameter of colonies derived from the 0 Gy control culture was about 670 μm. However, the diameter of EBs showed a radiation dose-dependent decrease (Figure 2).

In order to investigate the effect of ionizing radiation on gene expression, the differentiation-related specific gene expression detected in the initial iPS cells and EB cells was analyzed. The expression of the endoderm marker *Afp* in nonirradiated EB cells markedly increased to approximately 3 × 10^5-fold compared with that in the initial iPS cells. In contrast, a significant decrease was observed in the expression levels of the pluripotent stem cell markers *Nanog* and *Oct-4* and the mesoderm marker *Brachyury* compared with that in the initial iPS cells. In addition, no significant changes were observed in the expression of the ectoderm marker *Nestin* (Figure 3).

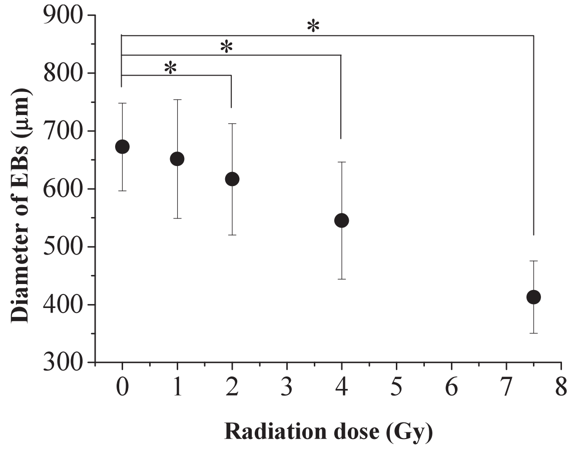

Figure 2. Diameter of EBs derived from iPS cells exposed to X-rays at 1–7.5 Gy. *$P < .05$.

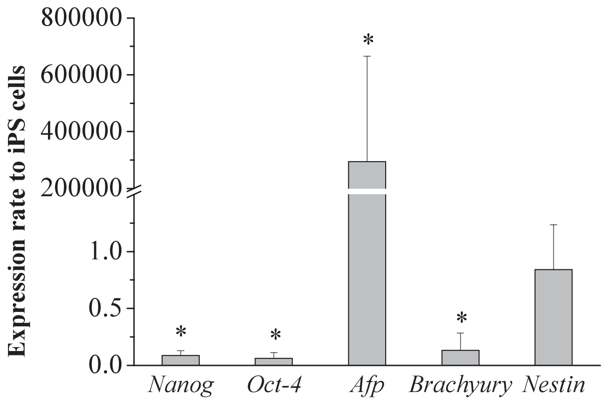

Figure 3. Differentiation-related specific gene expression detected in EB cells. *$P < .05$.

Next, the expression of these genes was analyzed in the EB cells derived from irradiated iPS cells. *Afp* expression significantly decreased in a radiation dose-dependent manner, showing a 0.19-fold decrease at 4 Gy and a 0.04-fold decrease at 7.5 Gy. In contrast, no significant difference was observed in the expression of other genes in almost all cases (Figure 4).

As a conclusion, our results show that iPS cells are less sensitive to radiation. Therefore, it suggests that the radiosensitivity of iPS cells is low to some extent. There is a difference in radiosensitivity in the early differentiation pathway of iPS cells to the three germ layers, with the sensitivity being highest in the differentiation pathway to endoderm.

Acknowledgments
This work was supported by KAKENHI, a Grant-in-Aid for Scientific Research (B) (No. 21390336 IK) and by a Grant for Co-medical Education Program in Radiation Emergency Medicine by the Ministry of Education, Culture, Sports, Science and Technology, Japan (2009, 2010). This work has also received support from a Grant for Hirosaki University Institutional Research (2008–2010).

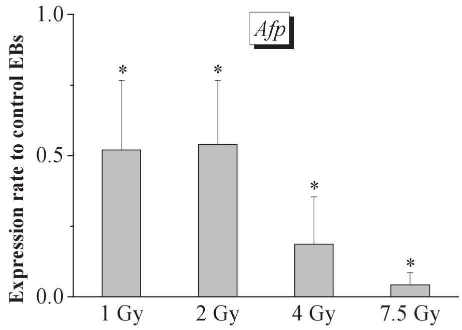

Figure 4. Behavior of differentiation-related specific gene expression detected in EB cells derived from nonirradiated and irradiated iPS cells. *$P < .05$

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Acute X-irradiation damages to the appearances and some visceral organs in mice.

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Abstract: To morphologically confirm acute radiation damage and organ radiosensitivity in mice, we performed whole body X-ray irradiation at single doses of 0 (control), 2, 4, 8, and 10 Gy. At doses of 8 and 10 Gy,body and thymus weights showed significant reductions in males. In addition, bleeding was found in the testes and intestine, head hairs fell out, and liver decolorization was observed. Furthermore, leucocytes in blood, spermatocytes in testes, and primary follicles in ovaries were decreased with doses of 2 and 4 Gy.

Key words: acute X-radiation damage, visceral organs, morphology, mouse

Introduction

X-radiation damage to various organs in humans and mice have been noted in radiological textbooks (Kiefer, 1990; Aoyama and Niwa, 2008). However, the morphological features of radiosensitive organs have not been widely reported, because most related experiments were conducted in the previous century. In the present study, we performed experiments with mice to investigate the morphological features of acute radiation damage.

Materials and Methods

ICR mice (7 weeks old 4 males, 4 females for each dose in two series) were exposed to whole body irradiation at 0 (control), 2, 4, 8, and 10 Gy using a Hitachi MBR-1505R2 (150 kV, 5 mA) at a dose rate of 0.133 Gy/minute. Therefore, the mice were kept at the Institute for Animal Experiments of Hirosaki University, and weighed and photographed daily in the first series, or every other day for 13 days in the second series after undergoing irradiation.

Ten and 13 days after radiation, the right kidneys, gonads (testes or ovaries), adrenal glands, and thymi were removed from half of the mice in each series, after examining the viscera and drawing blood from the heart. The extracted organs were preserved in 10% formalin and a 40% alcohol solution, then weighed and cut into 5-μm thick sections, and subjected to hematoxylin and eosin (H & E) staining. In addition, blood samples were

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exposed to Giemsa staining to count the number of the leucocytes in each slide in tissues exposed to the various doses of radiation.

Two male mice exposed to 10 Gy died on day 12 in the second series, thus their organs were weighed on that day and subjected to H&E staining, but no Giemsa staining was performed. In addition, blood samples were not obtained from two female mice exposed to 10 Gy in the second series.

Results

In comparison with the control mice, the body weights of the males were significantly decreased after a dose of at least 4 Gy from day 2 after irradiation, whereas the body weights of females were reduced only at doses of 8 and 10 Gy in a temporal manner from days 2 to 4 (Figs. 1, 2). Furthermore, thymus weights were decreased after doses of 8 and 10 Gy in males and at 10 Gy in females (Fig. 3), whereas the kidneys, adrenal glands, and gonads remained unchanged in regard to weight. In females, head hairs fell out after a dose of 10 Gy (Fig. 4). In addition, bleeding was found in the testes and in intestines, while decolorization was often found in the livers at dose of 8 and 10 Gy in the mice (Table 1, Fig. 5a-d).

Histological findings revealed that lymphocytes in the cortex of the thymus were decreased after doses of 8 and 10 Gy (Fig. 6a, b), while spermatocytes in the testes decreased with 2 and 4 Gy, and disappeared completely with 8 and 10 Gy in the males (Fig. 7a, b), and sperm volume was decreased with 10 Gy. Also, bleeding was found in the interstices between the seminiferous tubules and under the tunica albuginea after doses of 8 and 10 Gy (Fig. 7b). In female mice, the primary follicles in the ovaries were decreased and then disappeared with 4, 8, and 10 Gy (Fig. 8a, b). In contrast, no histological changes were recognized in the kidneys and adrenal glands in irradiated mice as compared to the controls. After doses of 2 and 4 Gy, the numbers of leucocytes were decreased to about half as compared to the controls, and disappeared after dosed of 8 and 10 Gy (Table 2).

Discussion

In the present study, body and thymus weights diminished in male mice after 8 or 10 Gy of irradiation. Furthermore, bleeding was found in the testes and intestines, while head hairs fell out and liver decolorization was observed. In addition, leucocytes in blood, spermatocytes in the testes, and primary follicles in the ovaries were decreased at least at 2 Gy of radiation. As for histological changes in the testes, ovaries, and thymi after irradiation, our results were largely similar to previously reported findings (Bloom, 1984).

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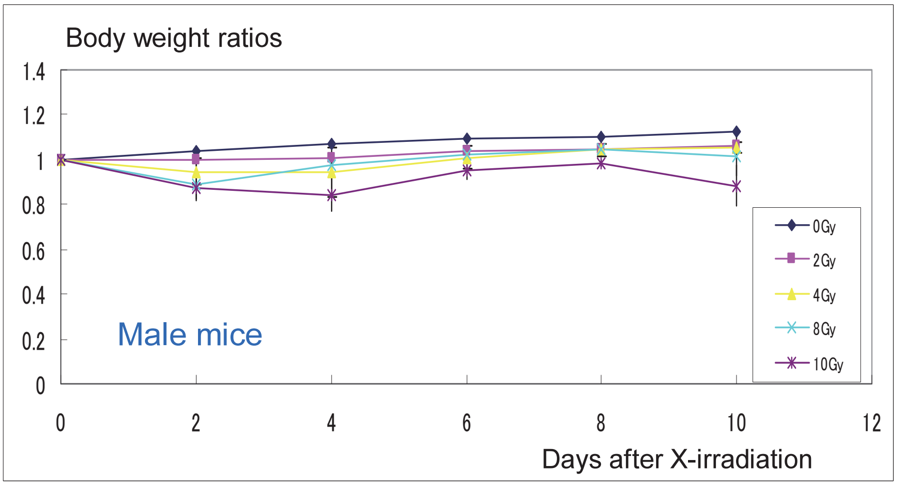


Fig. 1. Body weight ratios of male mice over 10 days after whole body irradiation. Body weights of male mice that received from 2-10 Gy were decreased from the 2nd day after irradiation and the decrease was significant in mice that received at least 4 Gy from day 4.

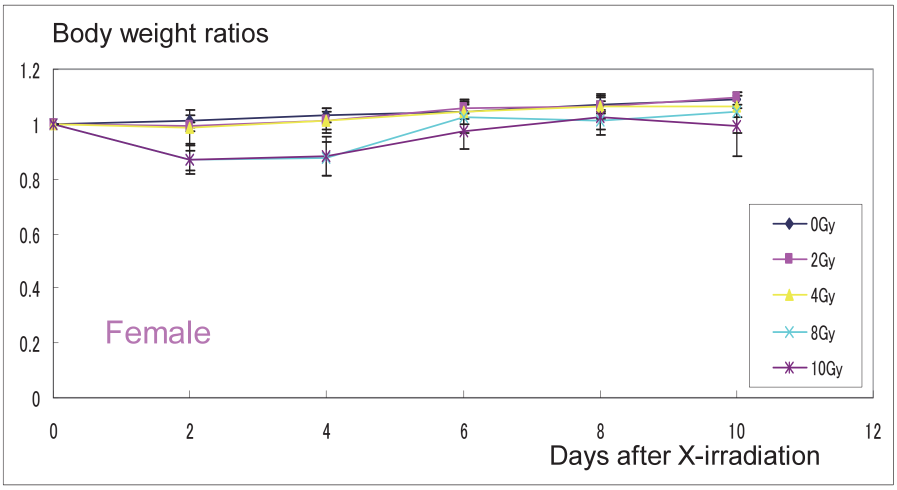


Fig. 2. Body weight ratios of female mice over 10 days after whole body irradiation of 0 to 10 Gy. Body weights decreases during first 4 days after irradiation were seen in female mice that received 8 or 10 Gy.

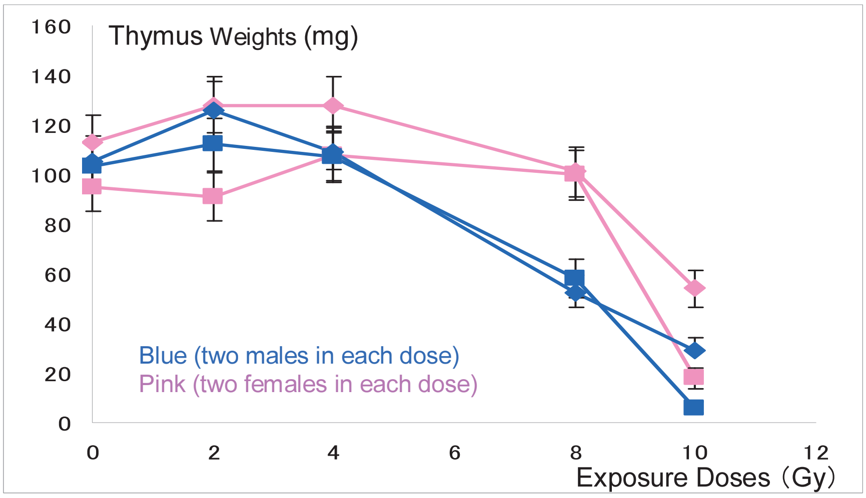
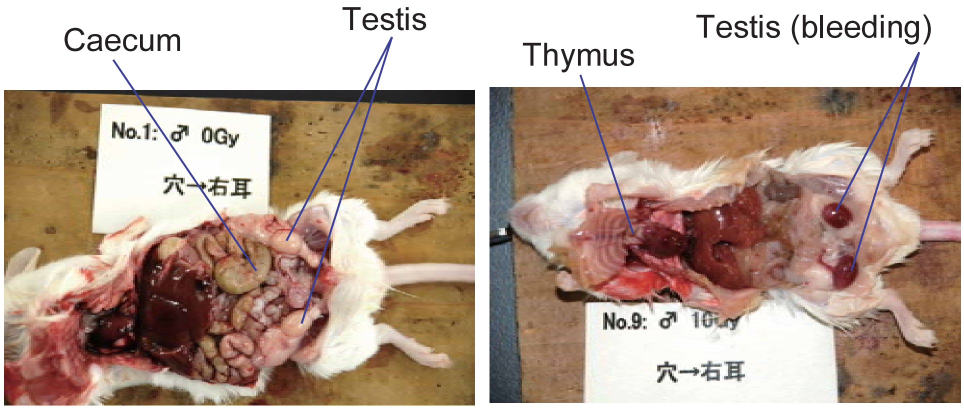


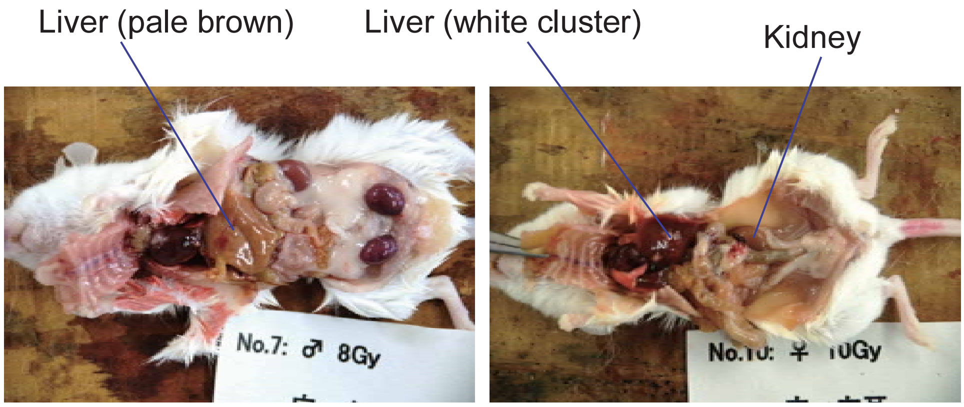
Fig. 3. In comparison with non-exposed mice, thymus weights decreased in males that received 8 and 10 Gy, and females that received 10 Gy of radiation.

Fig. 4. Representative image of hairs fallen out of head of female that received 10 Gy of radiation.



(a) Male at 0 Gy (b) Male at 10 Gy

Fig. 5a, b. Shown are representative thoracic and abdominal organs from male mice that received (a) 0 Gy or (b) 10 Gy of radiation. Bleeding was found in the bilateral testes and intestines of males that received 10 Gy.

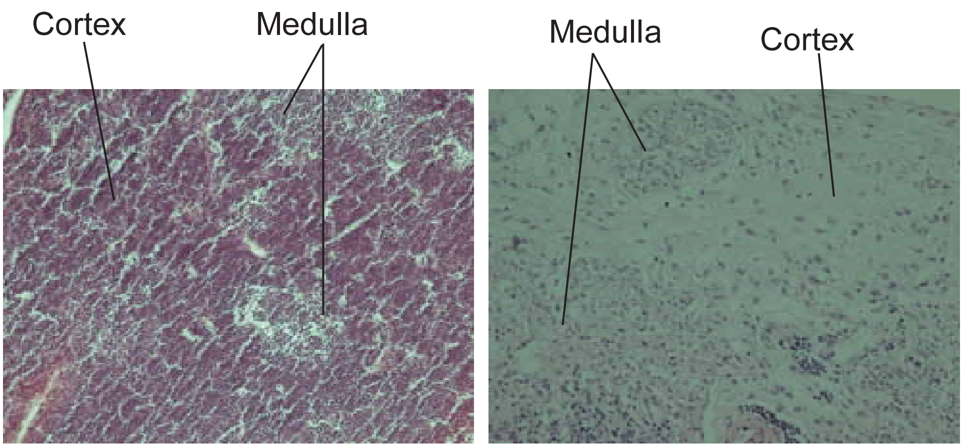


(c) Male at 8 Gy (d) Female at 10 Gy

Fig. 5c, b. Shown are thoracic and abdominal organs from (c) male and (d) female mice that received 8 and 10 Gy of radiation, respectively. Bleeding was found in the bilateral testes of the male, and in the intestines of both. Liver decolorization was often seen in mice that received 8 or 10 Gy.

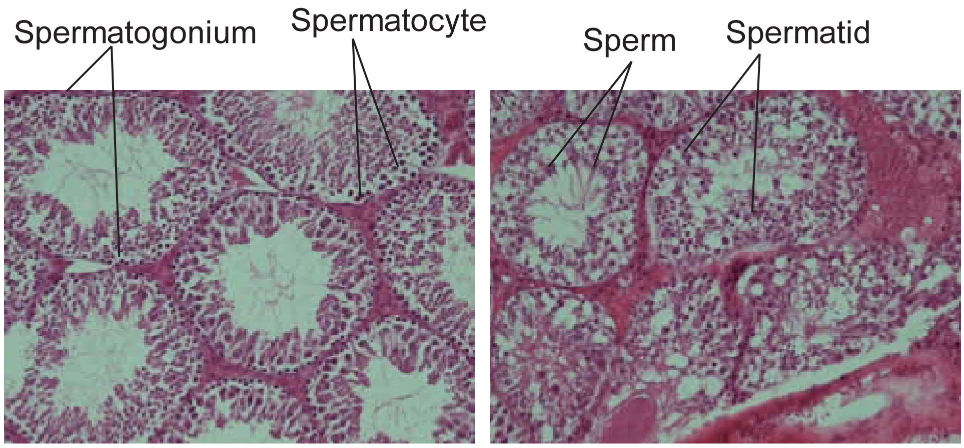
Table 1. Frequency of bleeding and liver decolorization in mice after irradiation at various doses.

Exposed at	Sexuality	Number	Bleeding of		Decolorization in Liver
			Intestine	Testis	
0 Gy	Male	4	0	0	0
	Female	4	0	0	0
2 Gy	Male	4	0	0	0
	Female	4	0	0	0
4 Gy	Male	4	0	0	0
	Female	4	0	0	0
8 Gy	Male	4	4 (100%)	3 (75%)	2 (50%)
	Female	4	4 (100%)		0
10 Gy	Male	4	4 (100%)	4 (100%)	0
	Female	4	4 (100%)		1 (25%)
Sum		40	16	7	3



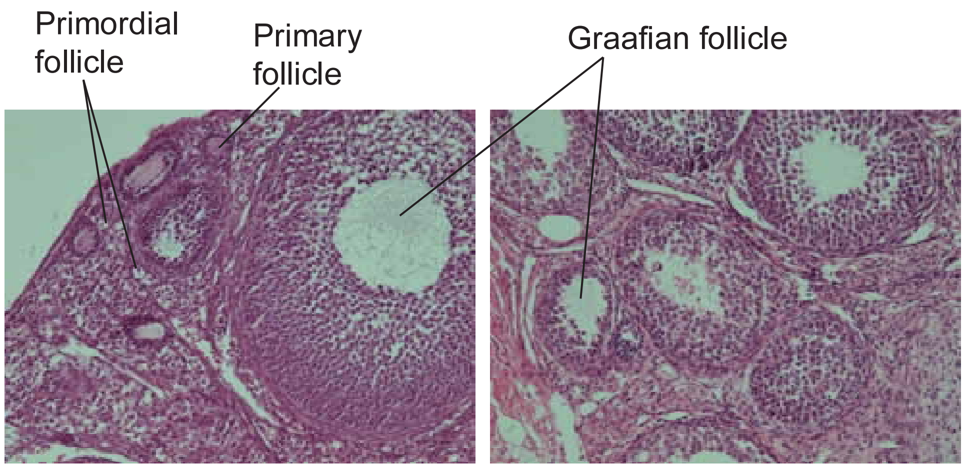
(a) Male at 0 Gy (b) Female at 10 Gy

Fig. 6a, b. Histological findings showed that the number of lymphocytes in the cortex of the thymus was decreased and later disappeared in mice that received 8 or 10 Gy of radiation. H&E staining. Magnification 100×.



(a) Male at 0 Gy (b) Male at 10 Gy

Fig. 7a, b. Spermatogonia and spermatocytes in the testes disappeared completely with 10 Gy of radiation, while sperm was decreased. Bleeding was found in the interstices between the seminiferous tubules at 10 Gy. H&E staining. Magnification 100×.



(a) Female at 0 Gy (b) Female at 10 Gy

Fig. 8a, b. Primordial and primary follicles in the ovaries were decreased and later disappeared with 10 Gy of radiation. H&E staining. Magnification 100×.

Table 2. Mean number of leucocytes counted in 10 areas after irradiation at various doses.

Exposed at	Sexuality	Date of drawing blood after exposure				Mean
		1st series		2nd series		
		10th	13th	10th	13th	
0 Gy	Male	23	21	10	20	18.5
	Female	6	11	8	13	9.5
2 Gy	Male	4	13	9	3	7.3
	Female	8	7	6	8	7.3
4 Gy	Male	3	4	2	1	2.5
	Female	7	1	4	6	4.5
8 Gy	Male	0	0	0	2	0.5
	Female	0	2	0	2	1
10 Gy	Male	3		0		1.5
	Female	1	2			1.5

Examination of urinary protease activity as a biomarker for evaluating effects of external irradiation of rats

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Abstract. We examined urinary protease activity after X-ray irradiation in rats to discover a protease that could to be function a biomarker for evaluating radiation exposure following radiation accidents, acts of nuclear terrorism, or major nuclear disasters. Rats were exposed to a single dose of 5-Gy irradiation, after which their urine was collected regularly for 7 days. In addition, the radiation dose was changed up to 4 Gy to examine the effects at different radiation levels. Zymography revealed that urinary protease activity markedly increased after 3 h of a single dose of 5-Gy irradiation. The protease activity of a protease with a molecular weight of 70 kDa increased after 6 h of irradiation, and then decreased in a time-dependent manner. The isoelectric point was approximately 5.0-6.2 on a two-dimensional zymography Significant increase in urinary protease activity was observed at a dose of 2-3- Gy irradiation, however a tendency to decrease was observed at a dose of 4 Gy. These results suggest that the protease activity of 70 kDa can function as a biomarker for time-course monitoring after external radiation exposure.

Key words: X- ray irradiation; urinary protease activity; zympgraphy

Introduction

The depletion of fossil fuels worldwide has tremendously increased the importance of harnessing nuclear energy. However it is crucial to be prepared to tackle emergencies from nuclear terrorism and other nuclear disasters.

To evaluate the effects of radiation exposure in such situations, a rapid and non-invasive screening test before chromosomal aberration analysis are required to identify the status of those exposed and decide on their courses of treatment.

Chromosomal aberration analysis, which has been established as the gold-standard in radiation dosimetry, is used for evaluating radiation exposure [1]. However, it takes at least three days before the results are available. Therefore, we have researched a new biomarker for evaluating the effects of radiation.

Effects of radiation differ for each internal organ, and renal injury has the potential to alter urinary protein profile [2]. Therefore, urinary protease activity might change in the same manner. A drawback of analyzing enzyme activity is that it easily decreases in poorly-preserved samples. However, enzyme assays are a highly sensitive, and thus, have been implemented by us in this analysis. To discover a protease that could be used as a biomarker for evaluating the effects of radiation exposure, urinary protease activity was examined in rats after whole-body X-ray irradiation.

Materials and methods

Whole-body irradiation and urine collection

Six-week-old female Sprague-Dawley rats were exposed to a single dose of 5-Gy irradiation, and their urine was collected regularly for 7 days. To

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examine the effects of the radiation dose, the dosage was increased to 4 Gy, and urine was collected 24 h after each treatment. Each urine sample was centrifuged at 800 × g and the supernatant was stored at -80ºC.

Zymography

Gelatin or casein zymography was performed according to the method of Miyazaki, et al [3] with some modification. In particular, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was performed using gelatin or casein; both are substrate proteins of proteases. The gel was then shaken in a buffering solution including Triton X-100 to remove SDS and renature the separated proteins. The gel was placed in a suitable buffering solution containing calcium ions and the substrate protein was digested using renatured protease after 16-18 h at 37ºC. When proteins in the gel ware stained with a protein dye, the area where the substrate was resolved by the protease was detected as a transparent band.

Two-dimensional gelatin zymography

Isoelectric focusing was performed using polyacrylamide gel in a urea-free buffer according to the method of Drysdale, et al [4]. The gel was then placed on SDS-polyacrylamide gel, and zymography was performed as mentioned above. Isoelectric point (pI) of the resultant transparent band was estimated from that of internal marker proteins.

Results

On gelatin zymography, urinary protease activity markedly increased 3 h after radiation exposure in the 5-Gy irradiation group compared with that of the non-irradiation group (Fig. 1A). Two types of proteolytic activities were detected; one decreased in a time-dependent manner and the other remained constant. Activity of 70 kDa increased 6 h after post-radiation exposure, and then decreased over time. Casein zymography showed a pattern of protease activity similar to that of gelatin zymography (Fig. 1B). These results suggest that the protease activity of 70 kDa can be a biomarker for time-course monitoring after radiation exposure and it has substrate specificity to casein as well as gelatin.

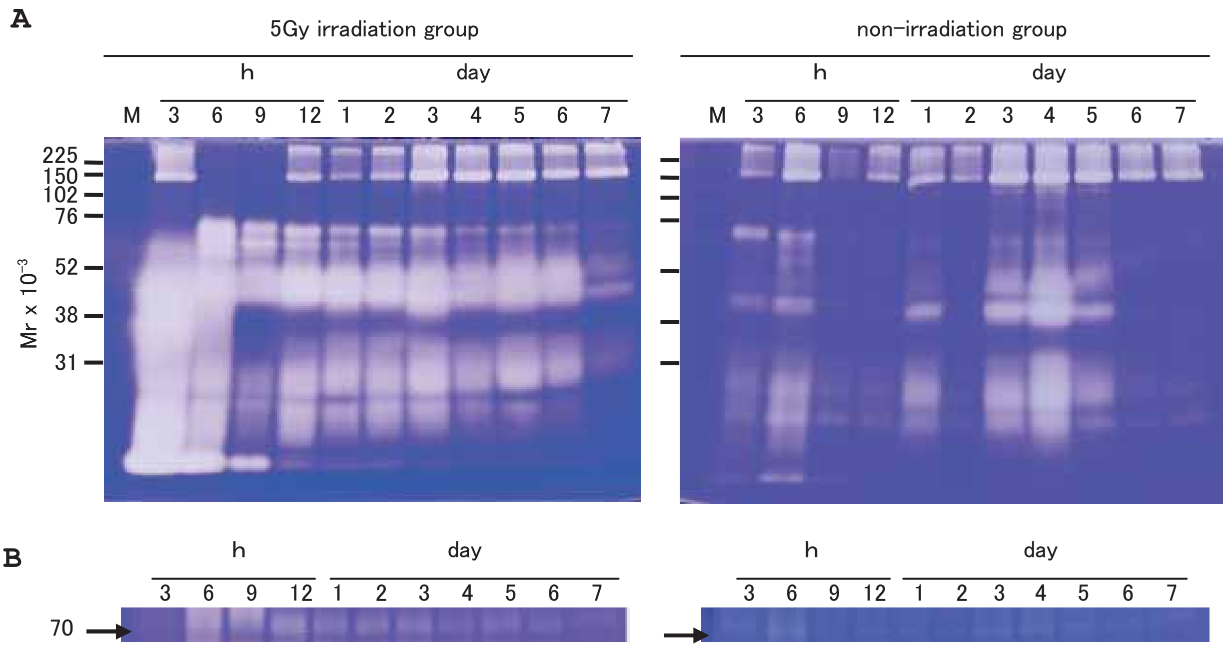

Fig. 1. Zymographic comparison of urinary protease activity in rats irradiated with of 5-Gy irradiation with that in non-irradiated rats. Rats were exposed to a single dose of 5-Gy irradiation, and urinary protease activities in samples collected post-irradiation were analyzed by zymography. Seven μl of each urine sample was diluted with 3 μl sample buffer before electrophoresis, and SDS-PAGE was performed with 10% polyacrylamide gel containing 0.1% gelatin or casein. M: molecular weight protein markers

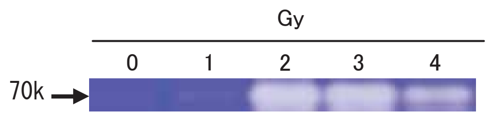

Fig. 2. Effect of different irradiation doses on to urinary protease activity in rat. Whole-body irradiation levels were changed up to 4-Gy irradiation, and urinary protease activities were analyzed by gelatin zymography in samples collected after 24 h.

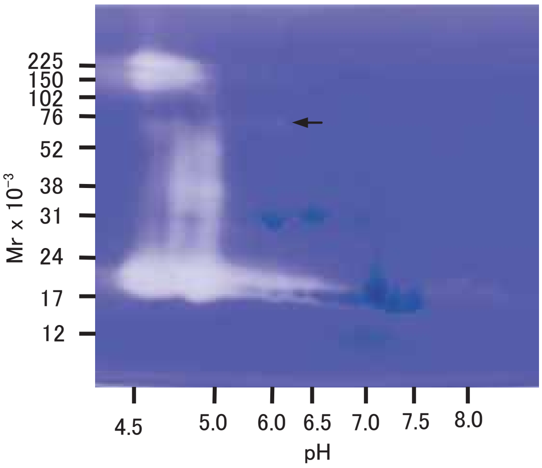

Fig. 3. Determination of pIs of urinary proteases in rats by two-dimensional zymography. Isoelectric focusing was performed under conditions without in a urea-free buffer urea in a low-temperature chamber; 0.1 M NaOH solution and 0.1 M H_2SO_4 solution were used as anode and cathode buffers, respectively.

The radiation dose was then changed up to 4 Gy to examine the effects of different radiation levels. At 1-Gy irradiation, urinary protease activity slightly increased. A significant increase in protease activity was observed at 2-3-Gy irradiation. However, a decreasing was observed at 4-Gy irradiation (Fig. 2).

Two-dimensional gelatin zymography was performed to determine pIs of urinary proteases, which was determined to be 4.5-5.0 in most proteases. The protease with molecular weight of 70 kDa had pI of 5.0-6.2 (Fig. 3).

Discussion

We examined urinary protease activity in rats to discover a biomarker that could be used to or evaluate effects of external irradiation. Zymography indicated marked increase in urinary protease activity 3 h after a single dose of 5-Gy irradiation. Whole-body irradiation is known to induce an increase in the number of urinary proteins and increased glomerular albumin permeability as early as 15 min post-irradiation [2]. In addition, ionizing radiation exposure and toxic stresses to cells induce activation of multiple MAPK pathways, which are involved in influencing protein expression and controlling cell survival and repopulation [5]. Because of those, significant increase in urinary protease activity was observed after 5-Gy irradiation.

Urinary activity of 70 kDa increased at 6 h after radiation exposure and then decreased over time. When the radiation dose was changed up to 4 Gy, the activity increased slightly at 1-Gy irradiation but increased significantly at 2-3-Gy irradiation. However, the urinary protease activity had tendency to decrease at 4-Gy irradiation, indicating increase in DNA damage and cell apoptosis. These results suggest that the urinary protease activity of 70 kDa can function as a biomarker for time-course monitoring after external radiation exposure. However, it is unclear whether it can be a marker for external radiation dose assessment or not. It needs to be validated by detailed research for radiation doses, especially below 2 Gy.

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Reconstitution of B-1a cells after murine allogeneic umbilical cord blood transplantation: A new advantage of the umbilical cord blood-derived hematopoietic system

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Abstract. The ability of murine allogeneic umbilical cord blood cells (UCBCs) to reconstitute the immune system was investigated. In RAG2(-/-)BALB/c mice, hematopoietic stem cells present among allogeneic UCBCs and bone marrow cells (BMCs) differentiated into phenotypically mature T cells, B cells, myeloid cells, and granulocytes. In addition, UCBCs and BMCs had essentially similar abilities for reconstitution of functional T and B lymphocytes even in an allogeneic environment, because both types of chimeric mice generated a specific antibody response to TNP-KLH as a T-dependent antigen and also rejected the third-party skin grafts. Furthermore, this study demonstrated that UCBCs have promising potential for reconstitution of B-1a cells, thereby replenishing bacterial polysaccharide-reactive IgM as a front-line defensive factor against invading pathogens. On the basis of our finding, we strongly recommend the use of UCBCs for hematopoietic stem cell transplantation.

Key words: **umbilical cord blood, hematopoietic system, radiation exposure**

Introduction

Umbilical cord blood cell (UCBC) transplantation has been applied as a strategy for treatment for accidental high-dose total-body radiation exposure [1]. In clinical situations, perfect major histocompatibility complex (MHC) matching cannot be expected in UCBC transplantation, which is based essentially on unrelated donor-recipient combinations. Although the low content of mature T cells allows the use of even MHC-mismatched UCBCs, the extent to which lymphocytes derived from MHC-mismatched UCBC transplantation recover their immune function remains unclear because of the lack of convenient animal models. To resolve this issue, we examined the functional maturation of lymphocytes derived from fully MHC-mismatched UCBC transplantation in a murine model system. In this study, we first found that B-1a cells [2-4], which produce natural IgM antibodies against pathogens such as *Streptococcus pneumoniae* and the influenza virus, can be generated from UCBCs but not from bone marrow cells (BMCs).

Survival rate and hematopoietic reconstitution after transplantation

To deplete NK cells, RAG2(-/-)BALB/c recipients were intraperitoneally administered rabbit anti-asialo GM1 antibody 1 day before transplantation. On the following day, the recipients were lethally irradiated at 8 Gy and then immediately given a transplant of T-cell-depleted allogeneic UCBCs or BMCs obtained from GFP-transgenic C57BL/6 mice. Survival rates of RAG2(-/-) BALB/c mice receiving high dose (1.0×10^6 cells), medium dose (0.5×10^6 cells), or low dose (0.1×10^6 cells) of allogeneic

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UCBCs or BMCs up to 16 weeks are shown. Almost all of the recipients in which UCBC and BMC transplantation were unsuccessful died within 3 weeks, as did control mice irradiated by X-ray without any transplantations. The survival rates of mice given medium- or high-dose UCBC and BMC transplants were similar (80-100%). Engrafted cells in the recipients' peripheral blood were analyzed by staining with antibodies against lineage markers such as CD3e (for T cells), B220 (for B cells), Mac-1 (for myeloid cells), and Gr-1 (for granulocytes). Flow cytometric analysis showed that the transferred allogeneic UCBCs and BMCs had developed into T cells, B cells, myeloid cells, and granulocytes in RAG2(-/-)BALB/c recipients. Every lineage was constituted of GFP positive cells, indicating that the cells were of donor origin.These results demonstrated that the capacity for self-renewal and the ability to differentiate into every hematopoietic lineage were essentially similar in both UCBCs and BMCs.

Function of UCBC-derived B cells

Antibody production by allogeneic UCBC- or BM-derived B cells was examined in the chimeric RAG2(-/-)BALB/c mice. Over 16 weeks after transplantation, the chimeric mice were immunized intraperitoneally with 2,4,6-trinitrophenyl (TNP) keyhole limpet hemocyanin (KLH) 2 biweekly, initially with complete Freund's adjuvant, and the second time without adjuvant. Two weeks after the second immunization, TNP antibody titer of their serum samples was determined by ELISA. As well as BMC-chimeric mice, both IgM and IgG antibody responses to TNP were successfully induced in UCBC-chimeric mice. These results demonstrating the ability of chimeric mice to elicit antibody responses to T-dependent antigen with Ig-class-switching confirmed that both B cells and helper T cells derived from allogeneic UCBC were immunologically competent.

Function of UCBC-derived T cells

The T-cell response to skin grafts was examined in the chimeric RAG2(-/-) BALB/c mice. Dermis for skin grafting was harvested from the tails of BALB/c, C57BL/6 and C3H/HeJ, and placed on the shaved back of the chimeric mice that had survived for more than 16 weeks after transplantation. Rejection time was determined as the day when the grafted skin became completely detached. On day 11 after skin grafting, UCBC- and BMC-chimeric mice rejected the third-party skin graft from C3H/HeJ mice, indicating the presence of donor-derived functional $CD8^+$T cells as well as $CD4^+$T cells. In contrast, skin grafts from BALB/c or C57BL/6 mice were still maintained in these chimeric mice on day 60. T-cell function of the chimeric mice was restricted by MHC from both C57BL/6 and BALB/c mice.

B-1a cell reconstitution in the peritoneal cavity

B cell population was composed mainly of three different subsets: B-1a, B-1b, and B-2 cells. Among these subsets, B-1a cells are generated from neonatal/fetal precursors and spontaneously secrete natural IgM antibodies against bacteria and viruses localized primarily in the peritoneal and pleural cavities. Peritoneal cells (PCs) were harvested from chimeric RAG2(-/-)BALB/c mice receiving allogeneic UCBCs or BMCs, and triple-stained with anti-B220, anti-IgM and anti-CD5 antibodies. Flow cytometeric analysis showed that the number of GFP-positive B-1a cells ($CD5^+B220^{lo}IgM^{hi}$) was high in normal BALB/c mice (45.3%) and UCBC-chimeric mice (20.9%) but low in BMC-chimeric mice (4.6%) (Fig.1A). Total IgM and bacterial polysaccharide(PS)-reactive IgM in UCBC- and BMC-chimeric mice were measured by ELISA(Fig.1B). The total IgM level was similar among the three groups, although bacterial PS-reactive IgM antibodies were produced predominantly in normal BALB/c and UCBC-chimeric mice in comparison to BMC-chimeric mice, indicating that the bacterial PS-reactive IgM production was correlated with the presence of B-1a cells. Whole PCs harvested from UCBC- and BMC-chimeric mice were individually transferred into the peritoneal cavity of RAG2(-/-)BALB/c mice (Fig.1C). The bacterial PS-reactive IgM was observed in the RAG2(-/-) mice that received PCs from normal

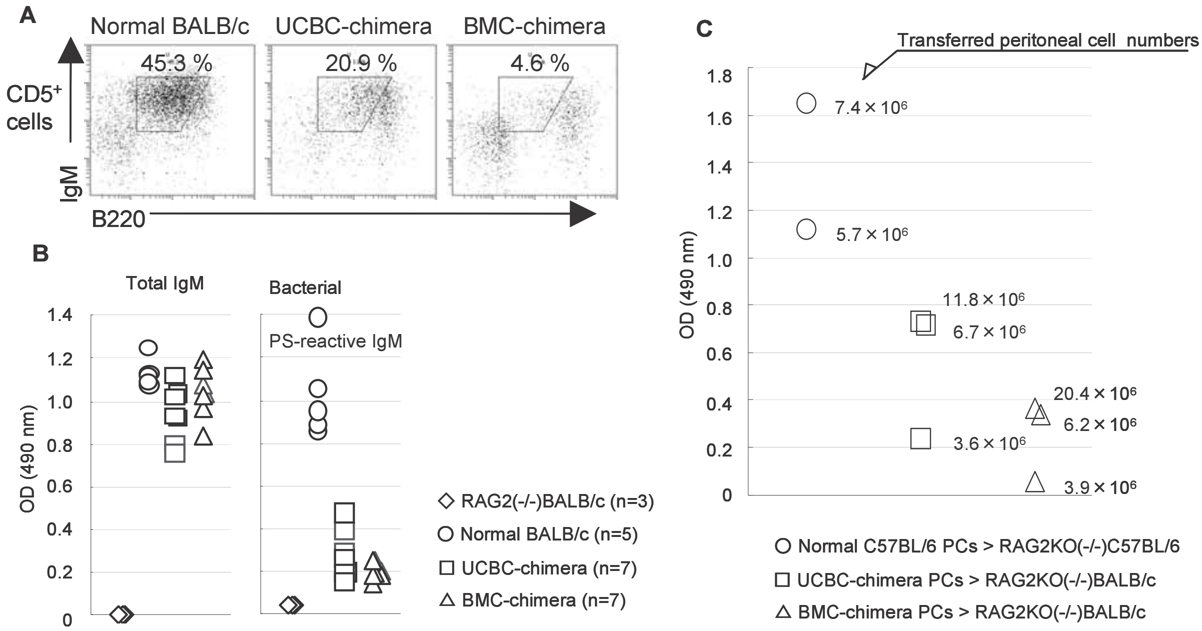

Fig. 1 . B-1a cell reconstitution in the peritoneal cavity

C57BL/6 and UCBC-chimeric mice, and the amount of bacterial PS-reactive IgM was dependent on the number of PCs transferred. In contrast, PCs from BMC-chimeric mice induced a marginal level of bacterial PS-reactive IgM in the RAG2(-/-)BALB/c mice. These results indicate that UCBCs have promising potential of natural IgM-producing B-1a cell reconstitution involving early innate defense.

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Characteristics of immune reconstitution by mixed umbilical cord blood transplantation in mice: Predominant engraftment of MHC-matched umbilical cord blood stem cell in recipients' bone marrow

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Abstract. The ability of mixed umbilical cord blood cells (UCBCs) to reconstitute the immune system was examined in this study. C57BL/6 recipients irradiated with a radiation dose of 9 Gy were transplanted with 3 different combinations of mixed UCBC. This study has clearly demonstrated the promising potential of transplantation of mixed UCBCs for achieving high survival rates and full immune reconstitution. We also found that in mixed UCBC transplantation, the major histocompatibility complex (MHC)-matched HSCs were predominantly engrafted in the recipients' bone marrow. Our future study should be solved the regulatory system, which permit engraftment of MHC-matched HSCs in the recipients' bone marrow.

Key words : **immune reconstitution, mixed umbilical cord blood transplantation, MHC, hematopoietic stem cell**

Introduction

Hematopoietic stem cell (HSC) transplantation has been applied for treatment of not only various hematological diseases [1-3] but also accidental high-dose total-body radiation exposure [4]. Currently, umbilical cord blood cells (UCBCs) are used as the primary source of HSCs for transplantation instead of bone marrow cells (BMCs). UCBC transplantation has several advantages over BMC transplantation, including the much larger size of the available donor pool, the rich proportion of hematopoietic progenitor cells, and the low content of mature T cells that might cause a graft-versus-host reaction [5-7]. However, the limited quantity of cord blood samples that can be obtained from a pregnant woman is considered to be a disadvantage of UCBC transplantation. To overcome quantity limitations, the use of mixed cord blood might be necessary. Due to the lack of convenient animal models, the analyses of the differentiation capacity of mixed UCBCs in recipients have been limited to clinical observations [8, 9]. In the present study, we evaluated the reconstitution and function of the immune system after mixed UCBC transplantation in mice.

Survival rates of the recipient mice after mixed UCBC transplantation

To deplete NK cells, female C57BL/6 [$H\text{-}2^b$] recipient mice were intraperitoneally administered rabbit anti-asialo GM1 antibody one day before transplantation. On the following day, the recipients, which had been exposed to a irradiation dose of 9 Gy, received transplantes of three different combinations of mixed UCBC {group [1] GFP-transgenic (Tg) C57BL/6 ($H\text{-}2^b$) and C3H/HeJ ($H\text{-}2^k$); group [2] GFP-Tg C57BL/6 ($H\text{-}2^b$) and BALB/c ($H\text{-}2^d$); and group [3] C3H ($H\text{-}2^k$) and BALB/c ($H\text{-}2^d$)}, each combination containing an equal number of cells. Mature T cells in UCBC were depleted by complement-dependent cytotoxicity using anti-CD4 and anti-CD8 antibodies. The survival rates of each group up to 16 weeks after transplantation are observed. The survival rate at 16 weeks after transplantation was 73% for group [1] (8/11 mice), 92% for group [2] (12/13 mice), and 75% for group [3] (3/4 mice). Five

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control mice that were irradiated but did not receive any transplantation died within 20 days. These results suggest that mixed UCBC transplantation can improve hematopoiesis in irradiated recipients.

Recovery of nucleated cell numbers in peripheral blood after mixed UCBC transplantation

After mixed UCBC transplantation, peripheral blood samples were collected from the recipients at 4-weeks intervals until 16 weeks. The recipient mice that died before 16 weeks after transplantation were excluded from this analysis. Nucleated cells were stained with Turk's solution and counted under a microscope. In all groups, the total number of nucleated cells began to increase rapidly at 4 weeks after transplantation and beyond, and reached normal levels at 12 weeks, indicating the development of a UCBC-induced hematopoiesis. Body-weight of living recipients in each group also showed an obvious increase, together with recovery of nucleated cells.

Characteristics of immune reconstitution by mixed UCBC transplantation

The chimerism of immune cells reconstituted at 16 weeks after mixed UCBC transplantation was detemined by flow cytometric analysis utilizing lineage-specific (against T-cells (CD3e), B-cells (CD45R/B220), macrophage (CD11b), and granulocytes (Ly-6G)) and MHC-specific (against H-$2K^k$ and H-$2K^d$) antibodies. GFP^+ lineage cells were found to have a C57BL/6 donor origin. Cells with a GFP^-H-$2K^{k-}$H-$2K^{d-}$phenotype were identified as immune cells derived from the C57BL/6 recipients' own X-ray-resistant HSCs. Bar graphs show the proportion of MHCs detected in the restructured-total immune cells of the recipients (Fig.1A-C). Flow cytometric analysis showed that in almost all recipients, the cell lineages had been reconstituted by GFP^+ cells and/or C57BL/6 recipients' own HSCs: group [1], 75% (6/8 mice); group [2], 100% (12/12 mice); group [3], 67% (2/3 mice). These results indicate the predominant engraftment of MHC-matched UCBC-HSCs in the recipients' bone marrow.

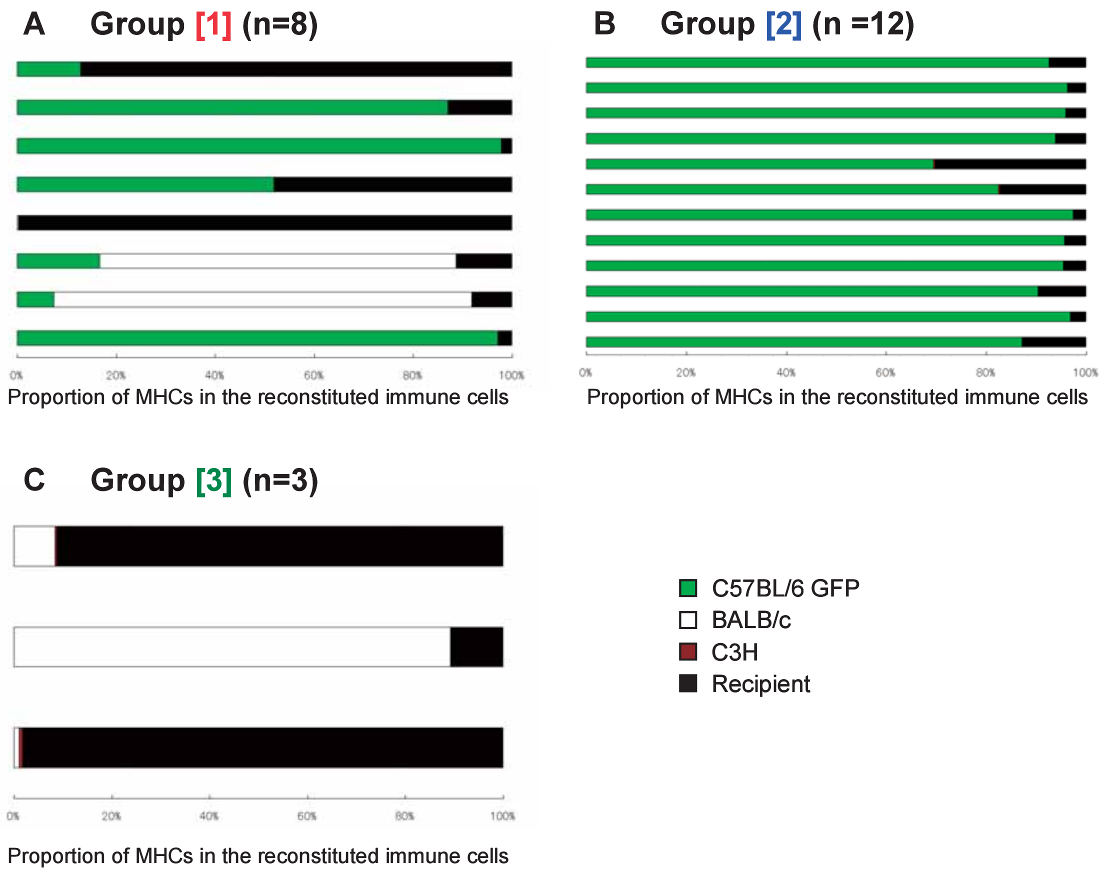

Fig 1. Characteristics of immune reconstitution by mixed UCBC transplantation.

For future studies

The following two questions should be answered in the future:

1. Is the immune system reconstituted by mixed UCBC transplantation functionally mature?
2. Which regulator permits engraftment of MHC-matched HSCs in the recipients' bone marrow?

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The 2010 Hirosaki University International Symposium

The Proceedings of The 2nd International Symposium on Radiation Emergency Medicine at Hirosaki University

平成23年３月12日　印刷
平成23年３月25日　発行

編　集　　弘前大学大学院保健学研究科
〒036-8564　弘前市本町66番地１

印刷所　　やまと印刷株式会社