Appendix

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PROCEDURES FOR THE MEDICAL APPLICATION OF RESEARCH REACTORS

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1. INTRODUCTION

The Kyoto University Reactor (KUR) is one of the four research reactors in Japan that are currently licensed for medical application, in addition to other research purposes. Taking the KUR as an example, legal and other procedures for using research reactors for boron neutron capture therapy (BNCT) are described, which are practiced in accordance with the "Provisional Guideline Pertaining to Medical Irradiation by Accelerators and/or Reactors, other than defined by the Medical Service Act" of the Science Council of Japan.

2. PROVISIONAL GUIDELINE

As a guideline for medical application of accelerators, nuclear reactors, etc., other than defined by the Medical Service Act, 1948, The Science Council of Japan issued a provisional guideline in 1978[1]. Pioneering clinical trials of BNCT had already begun, and the general therapeutic application of the MITR at Musashi Institute of Technology was about to take off. It is stated in the guideline that the parties concerned should realize the weight of social responsibility, and medical applications should be performed with a high standard of ethics. In principle the guideline requests that physicians should bear in mind the Helsinki Declaration, 1964 (as amended in 1975). Also, as to radiation protection, it is recommended to arrange the facilities and equipments in accordance with the ICRP Publication 26, 1977.

For medical irradiation, it is necessary to organize the followings.

(1) A Medical Team, composed of physicians and specialists, for planning and executing medical irradiation. The team should clarify its responsibility.
(2) A Specially Appointed Committee, for examining irradiation plans, giving necessary advice, and for evaluating and publishing the result of irradiation.

The procedures (protocols) for medical irradiation take the following steps.

(1) Those who propose to perform a medical irradiation should prepare a plan for the irradiation and submit it to the Committee for its approval. The irradiation plan should explain the followings in detail.

    a) Merits and demerits anticipated for the patient from the proposed irradiation.
    b) Radiation safety of the medical team.
    c) Bases for judging that the expected benefits for the patient are much greater than the demerits that may be incurred by the irradiation.
    d) Informed consent of the patient: The purpose, method, and anticipated outcome of the irradiation should be fully explained to the patient, and consent be obtained from the patient on his or her free will or from his or her representative who is capable of representing the will of the patient.
    e) Protocol for the clinical trial: Adaptability of the proposed irradiation and the irradiation plans should each be specified.
    f) Method of accurately evaluating the result of the irradiation.

(2) After the irradiation, its outcome should be reported as specified by the Committee.

(3) The Committee should evaluate the reported result or have it evaluated, and make it open.

Considering the social effect, the Medical Team and the Committee should keep a close contact with the related administrative offices of the central and the local governments, and pursue the irradiation under their understanding.

3. PROCEDURES AT KURRI

3.1 General

Since Research Reactor Institute of Kyoto University (KURRI) is a part of a national university, we are under the jurisdiction of the Ministry of Education, Science and Culture. At the same time, the KUR is regulated by the Science and Technology Agency (STA). In addition, the Ministry of Health and Welfare controls medical matters.

As a "collaborative research institutes belonging to national universities," all the research works performed jointly (or sometimes solely) by visiting researchers (in the present case by the "Medical Teams") at KURRI are done under the frame work of Collaborative Research. So the head of the Medical Team wishing to perform the medical trial should submit a "general" proposal for the coming fisical year. This "general" proposal is reviewed not by the Medical Committee, but by the Advisory Board of KURRI. In 1992, the Medical Committee requested that the cases should be restricted to malignant tumors with localized focus to substantiate the value of BNCT, and that the domicile of patients should be within an easy reach of the doctor (preferably within Japan) for easy post irradiation follow-ups. For the current FY 1994, proposals of five teams are approved, as shown in Table 1.

Table 1. Approved Proposals of Clinical Trials at KURRI (FY 1994)

Project Leader	Title
Prof. Satoshi Ueda (Kyoto Prefectural Univ. of Medicine)	Developments of boron compounds with high accumulation ratio to brain tumors and PET-BNCT system
Prof. Yoshifumi Oda (Kyoto Univ., Faculty of Medicine)	Development of boron compounds for BNCT and their clinical application
Prof. Yoshihiko Kotoura (Kyoto Univ., Faculty of Medicine)	Studies on the limb-preserving therapy for osteosarcoma by BNCT
Prof. Koji Ono (Kyoto Univ., Research Reactor Inst.)	Radiobiological analysis of the effect of BNCT on tumors and normal tissues
Prof. Yuzo Fujii (Lab. for Culture Collection, Inst. of Medical Science, Univ. of Tokyo)	Application of boronated anti-tumor immunoliposome to BNCT

3.2 Individual Clinical Trials

KURRI sets certain reactor operation days exclusively for medical irradiation. In FY 1994, seven days are designated as "medical," and no other experiments are performed on these days. Before performing medical irradiation using nuclear reactors, chief medical doctors who intend to perform BNCT should be authorized by the Prime Minister. Prof. Hiroshi Hatanaka was the first to be approved by the then Prime Minister Eisaku Sato in 1968. The review system for the authorization was requested and set forth by the then Prime Minister Kakuei Tanaka in 1974, and the items to be reviewed are:

(1) Name,
(2) Affiliation,
(3) Personal history, especially as related to BNCT, and
(4) Clinical experiences.

The review used to take about three mouths for each medical doctor, but recently the right of the authorization has been given to the "Medical Committee" of our institute. So far, ten MD's have been authorized as chief doctors.

The chief doctor should submit a proposal for ten days prior to the designated medical irradiation day. The proposal is reviewed by the Medical Committee this time, and the Director General of KURRI makes a decision. Then the President of Kyoto University notifies each treatment to STA five days before the irradiation. The notification includes:

(1) Date,
(2) Place,
(3) Reactor personnel on site the day of irradiation,
(4) Names of the chief medical doctor and the clinical staff,
(5) Patient (nationality, sex, age),
(6) Kind of tumor,
(7) Tumor location,
(8) Total neutron fluence, and
(9) Schedule for the day.

Also, the following items are attached:

(1) Condition of the reactor facility,
(2) Personal radiation control for clinical staff,
(3) Patient's record,
(4) Personal record of chief medical doctor,
(5) Detailed information on clinical staff,
(6) Past record of BNCT at the site.

3.3 The Medical Committee

Currently, the Committee consists of:

Director of Radiation Oncology Res. Lab., KURRI (Radiation Oncology, Chairman)
Prof., Biomedical Res. Center, Osaka Univ. (Radiology)
Prof., KURRI (Radiobiology)
Prof., Dept. Basic Medical Science, Tsukuba Univ. Medical School (Radiotherapy)
Prof., Faculty of Medicine, Kyoto Univ. (Dermatology)
Prof., Faculty of Medicine, Kyoto Univ. (Neurosurgery)
Prof., Chest Disease Res. Inst. Kyoto Univ. (Radiology)
Prof., Medical School, Osaka Univ. (Radiology)

Director, Research Reactor Div., KURRI (Physics)
Director, Radiation Control Div., KURRI (Physics)

There is a standing Medical Ethics Committee at Kyoto University which handles all medical matters at the School of Medicine, University Hospitals and related institutes. For general BNCT for malignant tumors there is no need to ask for the review of the Medical Ethics Committee, after it was first approved in 1987.

The doctor–patient relation is a matter of the medical doctor. The patient is duly hospitalized and registered at each hospital where the chief medical doctor for BNCT treatment is employed. KURRI however helps the doctor find appropriate local medical support, if necessary.

3.4 Report and Evaluation

A week after the treatment, all chief doctors must report to the Director General of KURRI about the status of the patient. Then the President of Kyoto University reports to the Science and Technology Agency about the treatment for each patient, including (1) Date and time, (2) Patient, (3) Neutron and gamma ray doses, (4) Dose of doctors, (5) Status of patient and others.

At the end of year, all doctors are invited to KURRI in order to report on and discuss the treatments performed at KURRI.

Also attending the annual review meeting are Professors of Dermatology, Radiation Oncology, and Neurosurgery of Kyoto University and other universities. Physicists, chemists, biologists and other interested scientists are also invited to attend, and the results of the performed medical irradiations are discussed from various view points.

4. CONCLUDING REMARKS

Procedures for clinical application of research reactors are described as currently performed in Japan, and more specifically at KURRI. Through scientific review of the performed clinical trials, future directions of this innovative treatment can be designed. It is felt that a more effort is desired before many procedural restrictions are lifted and clinical trials are to become fully–fledged practices.

Reference

1. T. Shibata, "On the establishment of 'Provisional guideline pertaining to medical irradiation by accelerators and/or reactors, other than defined by Medical Service Act' ", (in Japanese), Isotope News 7, 7–8, 1978.