5. Research Center for Charged Particle Therapy

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Overview:
The Research Center for Charged Particle Therapy has been carrying out medical practice and research using heavy ion beams generated from the HIMAC (Heavy Ion Medical Accelerator in Chiba) since 1994, as well as medical research on advanced diagnostic imaging techniques such as PET, MRI and CT. After clinical trials of carbon ion therapy had been carried out for various types of malignant tumors, the Center was successful in obtaining approval from the Ministry of Health, Welfare and Labor for its "Highly Advanced Medical Technology" in October 2003. The center offers the state-of-the-art therapy called "Charged Particle Therapy for Solid Tumors". Thus carbon ion therapy has meanwhile achieved for itself a solid place in general practice by accumulating the clinical experiences over a decade.

This year, as in previous years, a number of committees were organized to evaluate the eligibility of each patient to be treated with carbon ion therapy and to scientifically and ethically review the treatment results. The Multi-user utilization of the HIMAC has been successfully implemented for medical, biological and physics research. The biggest event of this year, the 10th Anniversary of the HIMAC was celebrated in July 2004.

Progress of Research:
1) Medical Practice and Research on Carbon Ion Therapy

The Center Hospital is unique in its position as a medical practice/research hospital even on a national scale, specialized in radiation therapy and diagnosis. It is equipped with a range of state-of-the-art diagnostic imaging equipment including CT, MRI, PET-CT, US and endoscopies on a scale and level well above those of a general hospital. The hospital has been also designated as Japan's Third Medical Facility functioning as a core medical place to provide emergency services for accidental radiation exposures. It has been actively engaged in establishing and maintaining a service outfit in readiness for radiation exposure accidents, jointly with the Research Center for Radiation Emergency Medicine. To fulfill the above role, the hospital has both outpatient and inpatient wards as well as a full complement of pharmacies and clinical laboratories to well above normal standards.

An extensive amount of medical information has been obtained from the clinical trials on carbon ion radiotherapy including diagnostic images and medical records. In an effort to achieve higher levels of sophistication, these clinical data has been systematically classified and standardized to establish data access methods based on a unified system of data management. This year, medical records and diagnostic images stored in the data-servers were first put into practice as an on-line service for evaluation of staging diagnosis and quantitative and objective assessment of the efficacy and side effects after treatment.

2) Clinical Results of Carbon Ion Therapy

As of February 2005, the number of patients registered was in excess of 2,000. Experiences to date indicate that carbon beam therapy is advantageous, ①by histology, to adenocarcinoma, adenoid cystic carcinoma and sarcoma (malignant melanoma and bone/soft-tissue sarcoma); ②by tumor origin, to skull base, head and neck, lung, liver, prostate, bone/soft tissue, and pelvis; ③by location, to tumors located in the vicinity of critical organs such as the eye, spinal chord, digestive tract with irregular shape. Tumors that infiltrate or originate in the digestive tract, however, appeared difficult to control with carbon ions alone.
The patient load continues to rise incessantly year after year, due not only to the way in which the irradiation techniques have been established but also as a result of the significant reduction in the number of fractions per patient. There is a rationale to justify the use of short-course RT due to the superior dose localization and the unique biological property of carbon ions. This has been proved in treatment of early stage lung cancer and hepatoma, where the fraction number has been successfully reduced to 1-4 fractions in 1-7 days. Even in prostate cancer and bone/soft tissue tumor, treatment has been performed using 16 to 20 fractions in 4 to 5 weeks with acceptable morbidity, roughly half the number of fractions required in the case of other conventional radiotherapy. This means that the facility can be operated more efficiently, offering treatment for a larger number of patients than is possible with other modalities over the same period of time. Currently, the number of irradiation sessions per patient averages 13 fractions over three weeks in carbon ion therapy.

Papers have been published on original work with lung cancer, liver cancer, head and neck cancer, and bone/soft tissue tumor. In addition, there have also been growing numbers of invitations for special lectures as well as interviews by the media.

3) Development of a Compact Accelerator:

The Department of Accelerator Physics and Engineering is in charge of regular operations, maintenance, and management of the HIMAC, which has been used for carbon ion therapy in the daytime and for biological and physics research at night. Research has been focused on the basic principle and technology of heavy ion accelerators and on the development of methodologies and devices for cancer therapy. During this fiscal year, major activities have been concentrated on R&D of a compact carbon therapy accelerator.

The injector system of the compact accelerator consists of two 10GHz permanent magnet ECR sources, RFQ linac, and IH type drift tube linac. Operation frequencies of both linacs were chosen at the same value of 200 MHz. APF (Alternating Phase Focusing) structure was adopted for both transverse and longitudinal focusing in the IH linac. The APF-IH linac structure has long been studied theoretically and experimentally because of its high energy efficiency and easiness in operation. This type of linac, however, has never been put to practical use since time-consuming model studies are required to fix cavity geometry. The RFQ and APF-IH linacs will be installed at NIRS by the end of 2005, and beam tests will be done using the 10 GHz permanent magnet ECR source. A cobalt based amorphous core was found to have high permeability approximately twice that of a typical magnetic alloy, FINEMET, core. We have developed this type of amorphous core to be used in the RF cavity for a synchrotron. Due to its excellent RF characteristics of high shunt impedance and low quality factor, a cobalt-based amorphous-core loaded RF cavity covers a wide frequency range without any tuning elements to keep its high-energy efficiency. The beam delivery system of this machine should be designed to realize a residual range of 250 mm with the carbon energy of 400 MeV/u and an irradiation-field diameter of 220 mm at maximum with a port length of 5.5 m. For this purpose, a spiral-wobbler method has been proposed.

4) Physical and Biological Aspects of Heavy Charged Particles

The Department of Medical Physics is researching physical aspects of carbon ion therapy and PET scans and is responsible for services supporting them with other departments of the Center. The Department has been supporting clinical trials on heavy ion therapy including the quality assurance (QA) and quality control (QC) services, treatment planning, and fabrication of treatment devices such as compensating filters and patient collimators employed for carbon ion therapy. These have been done in collaboration with the Hospital and the Department of Accelerator Physics and Engineering. This year significant progress has been made in the customization of devices to suit an increased number of patients.

Heavy-ion Radiobiology Research Group has done studies to evaluate the optimum fractionation regimen for carbon ion therapy and to develop methods for identifying the types of tumors suited to carbon ion radiotherapy. In the study on radiation-induced chromosome aberrations in patients who received radiotherapy, no difference was found between carbon ions and x-rays. It was found that in patients with malignant melanoma the anti-tumor effect was enhanced with combined use of Lonidamine, a mitochondria-targeted drug. In the animal study on memory disturbance after irradiation, correlation was found between the degree of disturbance and the brain weight. It was found that beer had a protective effect against radiation and this anti-radiation effect was due to a pseudo-uridine microchemistry. The Group has also engaged in an inter-facility comparative study by investigating biological effects between the beams used at the HIMAC and GSI.

5) Medical Imaging Research

Medical imaging research has been directed to the promotion of cancer radiotherapy and biological
function imaging with respect to oncology and neurosciences. This year, a preparatory study was aimed at next year's acquisition of a COE grant-in-aid in the field of molecular imaging technology for visualizing biological functions in the body.

As in previous years, a variety of multi-purpose automatic synthesizers and control apparatuses for manufacturing and synthesizing a diverse range of radioactive drugs have been developed, and methods for their use have been tested and proven. Various kinds of molecular probes have been developed for the purpose of imaging hypoxic cells, heart muscles and a particular part of intracerebral activity. In the research activities related to diagnostic machines, the major parts of a 4-D X-ray CT machine and a next-generation PET system were successfully developed.

Regarding the research on MRI (Magnetic Resonance Imaging), the achievements include developing dynamic MRI to demonstrate changes in the pharmacokinetics of Gd-DTPA in experimental tumors after charged particle irradiation, 3-D T1 imaging for quantitative evaluation of articular cartilage degeneration, MRS (magnetic resonance spectroscopy) for diagnosis of temporal lobe epilepsy, and proton MRI method for detecting a small degree of non-uniformity in dialysate flow in a hollow-fiber dialyzer.

6) Medical Exposure Assessment
To determine the "risk of cancer from diagnostic x-rays," estimation of exposure dose has been carried out on Japanese patients subjected to diagnostic examinations. This year, measurements of the exposure dose were performed on patients who had MDCT (Multi-Detector CT) and dental x-ray pictures as well as on patients and operators during IVR (Interventional Radiology).

7) Brain Imaging Project
The research has been focused on mental disorders and functional brain imaging using PET and MRI. In the study of the mechanism of mental disorders, the abnormal neurotransmission in the brain appeared to be related to mental disorders such as schizophrenia and mood disorders. It is known that some drugs for treatment of mental disorders work on the receptor. It was found that the receptor occupancy could be measured by antipsychotics and antidepressants in PET scans. It is essential to develop new promising ligands for PET research. In this regard, we have developed new radioligands for NMDA receptors and peripheral benzodiazepine receptors as an imaging tool of glial cells in the brain.