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Journal of Nuclear Materials 248 (1997) 360–368

journal of nuclear materials

Medical and other applications of high-energy heavy-ion beams from HIMAC

T. Murakami *, H. Tsujii, Y. Furusawa, K. Ando, T. Kanai, S. Yamada, K. Kawachi

Research Center of Charged Particle Therapy, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263, Japan

Abstract

A heavy-ion synchrotron facility, HIMAC (Heavy Ion Medical Accelerator in Chiba), began operating in 1993 at the National Institute of Radiological Sciences, Japan. The primary purpose of HIMAC is to carry out a clinical studies of 'cancer treatment using heavy ion beams'. Treatment employing carbon beams began in June, 1994, and about 150 patients had been treated by the end of July, 1996. The accelerator of HIMAC, which comprises linear accelerators as an injector and a synchrotron, can accelerate ion beams ranging from helium to argon with a maximum energy of 800 MeV/ nucleon for ions with a charge-to-mass ratio of 1/2. The research activities at HIMAC are not limited to medical applications, but include a wide area of research: physics, chemistry, biology, engineering, etc. © 1997 Elsevier Science B.V.

1. Introduction

Heavy ion beams have excellent properties for being applied to cancer treatment: a large biological effectiveness and good dose localization. A clinical study was, however, carried out at Bevalac, LBL, on a limited scale. To investigate both the effectiveness and extent of heavy ion therapy, a medical accelerator, HIMAC (Heavy Ion Medical Accelerator in Chiba), was constructed at the National Institute of Radiological Sciences (NIRS), Japan, in 1993 [1].

The accelerator of HIMAC comprises ion sources, an injector, a synchrotron with two identical rings, and a beam-transport system. The accelerator can accelerate ion beams ranging from helium to argon, with energies from 100 to 800 MeV/nucleon for q/A (charge-to-mass ratio) $= 1/2$ ions; silicon beams having the maximum energy can penetrate a range of 30 cm in tissue.

Accelerators which can deliver heavy ion beams with energies of around a few hundred MeV/nucleon are very scarce in the world. Thus, applying HIMAC beams to basic research without interfering with HIMAC's primary research, the clinical studies, was strongly desired. High-quality treatment on the other hand requires detailed knowledge concerning beam-material interaction processes. Thus, basic science programs involving researchers both inside and outside of the institute started in the fall of 1994.

A characteristic of the research activities at HIMAC is its broadness of the research areas (radiology, nuclear physics, atomic and molecular physics, radiation chemistry, engineering, and biology) in addition to the medical applications. Associated researchers are thus not necessarily users accustomed to conducting ion-beam experiments, except for some physicists. Cooperation between different disciplines, however, has proved to be very productive. Some of the research programs presently being carried out at HIMAC, including clinical studies, are reviewed in this report.

2. Accelerator and irradiation rooms

2.1. Accelerator structure

Fig. 1 gives a bird's-eye view of the HIMAC facility. HIMAC comprises ion sources, an injector, a synchrotron, a beam transport system, three treatment rooms, and four experiment rooms. A large part of the accelerators was

* Corresponding author. Tel.: +81-43 251 2111; fax: +81-43 251 1840; e-mail: murakami@rikvax.riken.go.jp.

PII S0022-3115(97)00135-9

Table 1
Medical requirements

Particle species	He, C, Ne, Si, Ar
Penetrating range	30 cm in tissue
Dose rate	5 Gy/min.
Max. field size	22 cm in diameter
Beam direction	vertical and horizontal

constructed 20 m underground, because the facility is located in a densely populated area.

The medical requirements are listed in Table 1. The accelerator is inevitably a complex one, comprising an injector with two types of linear accelerators, a synchrotron and a long beam-transport system, to fulfil the requirements. A brief outline of the facility is given in Table 2.

Two types of ion sources (ECR and PIG) are in operation. The former is superior in producing highly charged ions, while the latter is better in producing intense beams. The injector comprises two types of linear accelerators, an RFQ linac and an Alvarez linac (DTL). The linear accelerators use a radio frequency of 100 MHz with peak powers of 0.3 MW (RFQ) or 1.0 MW (DTL) for accelerating beams. A combination of two types of linear accelerators increases the energies of heavy-ion beams up to 6 MeV/nucleon, corresponding to 11% of the light velocity. Downstream of the DTL, the beams pass through a carbon-foil stripper to become fully stripped ions, which are injected into the synchrotron.

The synchrotron has two identical rings (upper and lower) which accelerate beams alternatively. The beams from the injector are deflected by using a pulse-operated magnet, and are injected into the two rings, alternatively. A typical rate of repetition of the cycle (injection, acceleration, and extraction of the synchrotron) is 2 or 3.3 s. The beam-spill length varies from 0.3 to 2 s, depending on the repetition rate. A beam transport system delivers the beams from the two synchrotron rings to the treatment rooms or experiment rooms, while changing courses according to a

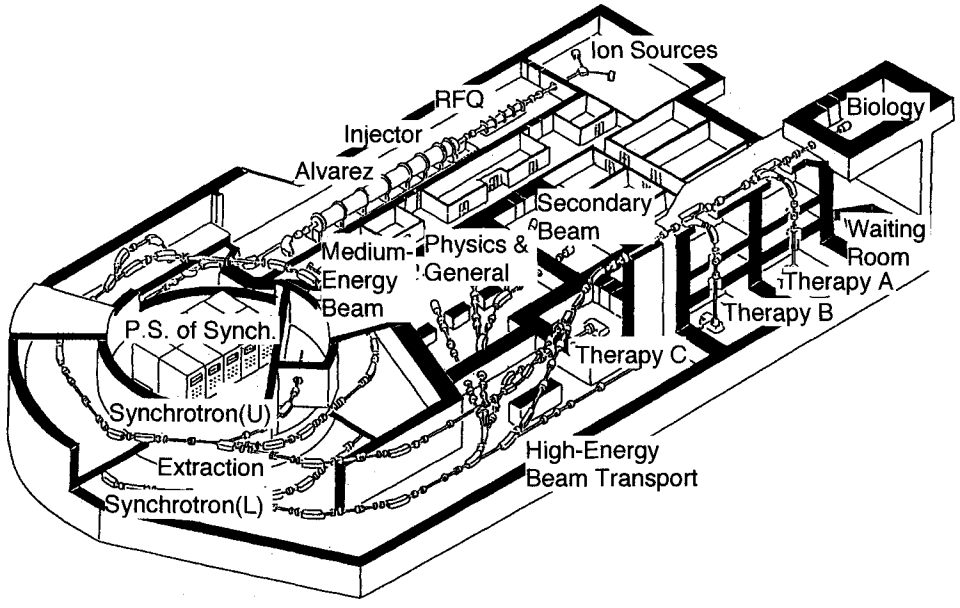

Fig. 1. Illustration of a bird's-eye view of the HIMAC facility.

Table 2
Outline of the facility

Ion source	PIG and ECR	8 keV/nucleon
Injector	RFQ linac (0.6 m ∅ × 7.3 m l)	800 keV/nucleon
	Alvarez linac (2.2 m ∅ × 24 m l)	6 MeV/ nucleon
Main accelerator	synchrotron (129.6 m in circumference)	100–800 MeV/nucleon
Irradiation rooms	3 treatment rooms	
	4 experiment rooms	

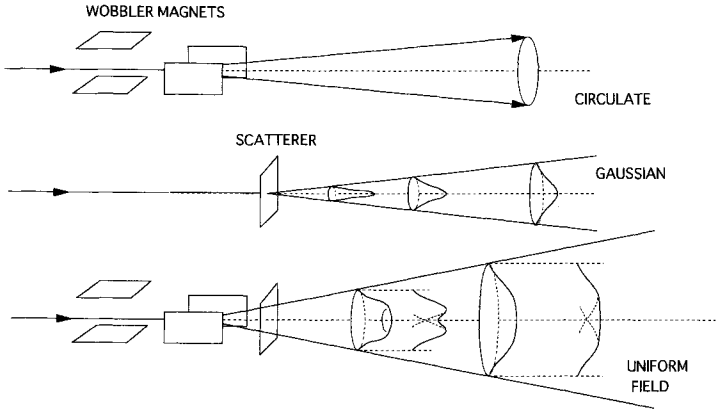

Fig. 2. Wobbling system to obtain a large and uniform irradiation field. A pair of wobbling magnets and a scatter enlarge the beam size.

schedule. During a treatment, the beam energies and beam courses are frequently changed. It typically takes 1 h for an energy change and 15 min for a course change.

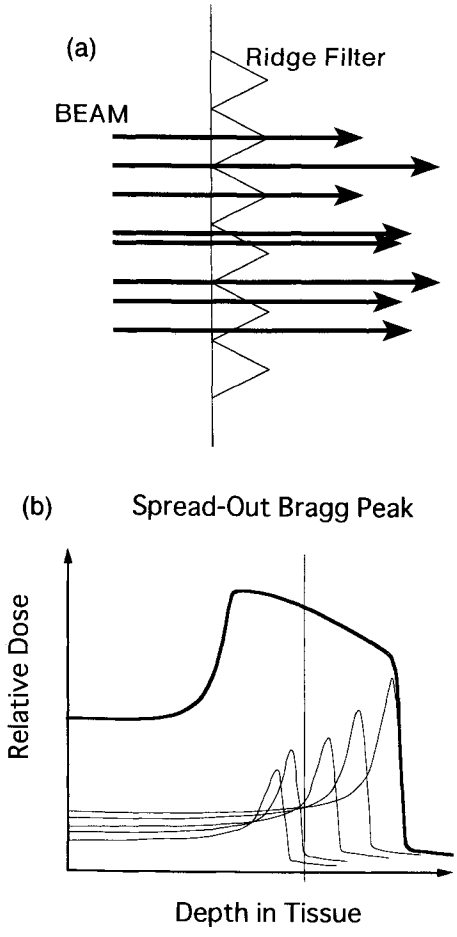

Fig. 3. (a) Ridge filter and (b) resulting SOBP. The ridge filter is an energy absorber with a triangular shape. The beam energy differs depending on the position after passing through the filter, and overlapped beams result in a broadened peak (the thick line).

2.2. Treatment rooms

There are three clinical-treatment rooms, equipped with horizontal (rooms B and C) and vertical courses (rooms A and B). Each course has a wobbling system designed by Kanai et al. [2]. A pair of AC-operated magnets and a scatter produce an irradiation field that is uniform within $\pm 2\%$ with a maximum size of 22 cm in diameter (Fig. 2). A block collimator and a multi-leaf collimator define the cross-sectional shape of the beam.

A ridge filter, as shown in Fig. 3a, is used to spread the Bragg peak so as to obtain a broadened peak, called a Spread-Out-Bragg-Peak (SOBP), such as shown in Fig. 3b. Thus, the thickness of the irradiation field is adjusted by the ridge filter and a compensator. A range shifter precisely controls the beam range.

2.3. Experiment rooms

Four experiment rooms for basic research have been prepared: (1) biology (BIO), (2) physics and general purpose (PHY), (3) medium energy beam (MEXP), and (4) secondary beam (RIB).

In the BIO room, irradiation experiments using cells or small size animals are carried out. The same wobbling system as that used in the treatment rooms has been installed in BIO to offer the same beams as those of the treatment rooms. The irradiation room of PHY is fortified by heavy radiation shields so that one can handle beams of maximum energy and intensity. In the MEXP room, beams of 6 MeV/nucleon from the injector are available. The beam-spill length can be varied between 1 and 700 μs by using a pulse-width-control system installed upstream of the RFQ. Since a switching magnet, which bends the beam to the MEXP course, is operated in a pulsed mode, the injector can deliver beams to both the synchrotron and MEXP alternatively. Considering the two ring structure of the synchrotron, three user groups can share the beam time. The RIB room will utilize secondary beams, and is presently under construction.

3. Research activities and operational schedule

Since the research activities of HIMAC extend over wide areas of research fields, it is convenient to categorize them into some groups. First of all, they are divided into two parts: clinical trials and basic research. The former involves the treatment of patients: medical doctors are in charge of the study. The latter includes many disciplines, and can be divided into a few categories: (1) irradiation methods and diagnosis, (2) biology, and (3) physics and engineering. It should, however, be noted that these categories are closely related: for example, the first topic, 'Irradiation corrected for the respiration motion' (described later), was carried out in cooperation with medical physicists, accelerator physicists, and medical doctors. The number of the proposed experiments is nearly 100, and about 300 researchers are participating in the program.

HIMAC is operated 24 h per day from Monday through Saturday. The day time (from 9:00 to around 20:00) from Tuesday through Friday is devoted to clinical trials or related data compilation. Monday is dedicated to a weekly inspection, the conditioning of new beams, and the technical training of operators. Experiments on basic research are carried out during the night and on weekends.

4. Clinical studies

The present clinical studies employ carbon beams with energies of 290, 350, and 400 MeV/nucleon. Beams of C^{4+} supplied by the ECR ion source are accelerated by the injector up to 6 MeV/nucleon, and pass through the carbon-foil stripper to be fully stripped. About 250 μA of C^{6+} beams are provided to the synchrotron.

Precise positioning of patients takes from 20 to 30 min, while beam irradiation continues for 2 min or less in typical cases. The treatment sites include the brain, head and neck, lung, liver, prostate, and uterus. Each patient is irradiated three times every week, and the treatment continues for 6 weeks.

5. Basic research

5.1. Development of irradiation and diagnosis methods

5.1.1. Irradiation corrected for the respiration motion

Some of the human organs such as the lung and liver change position by as much as 1 cm along with the autonomous respiration motion of patients. This movement results in a large margin of the target volume in the treatment planning and an unnecessary exposure of normal tissue. The irradiation corrected for this respiration motion is very effective in reducing excess irradiation. A new method developed by Minohara et al. [3] has been applied to treatments from June, 1996.

This irradiation method comprises the following steps. (1) An X-ray scanner was modified to scan images synchronized with the respiration motion of patients to allow an accurate planning. (2) The respiration motion is monitored by sensors attached to the patient's body during beam irradiation. (3) The beam spill is controlled so that the beam irradiates a target while the sensor position is within predetermined position. As soon as the sensor position is outside an approved range, the beam is quickly stopped. The timing relation is schematically shown in Fig. 4.

5.1.2. Auto-activation

A treatment planning utilizes CT values obtained by CT scanners and their calculated water-equivalent length. Thus, some ambiguity remains in the planning due to the complex structure of human bodies. If the treated volume can be confirmed, the reliability of the treatment planning

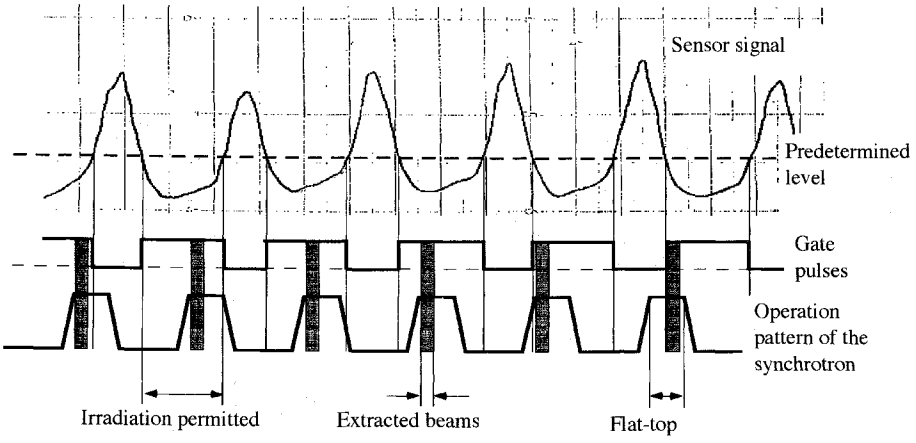

Fig. 4. Timing relation of irradiation corrected for the respiration motion. The predetermined level of the sensor signal produces gate pulses. Since the beam can be extracted during the flat-top, the beam is extracted when two signals overlap.

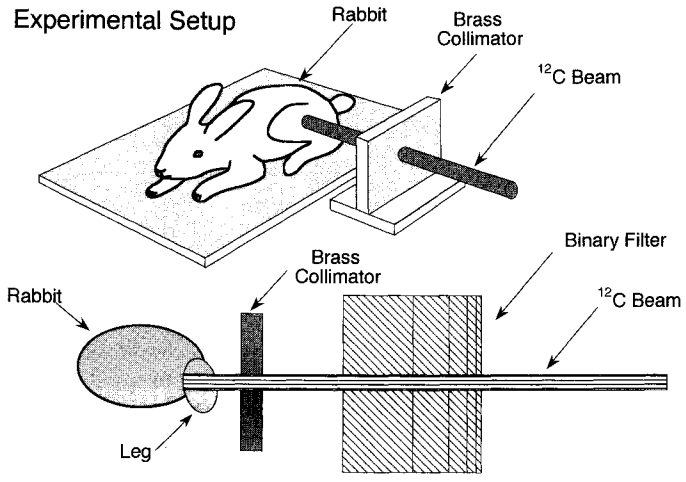

Fig. 5. Set up of the auto-activation measurement.

is greatly increased. One of the possible methods is auto-activation: a measurement of the distribution of positron emitters produced by the nuclear reactions using the positron-emission-tomography (PET) technique.

Following the observation of the auto-activation inside inorganic materials, experiments using a rabbit were carried out by Tomitani et al. [4]. The experimental set up is shown in Fig. 5. The induced activities of ^{11}C produced by the ^{12}C beams were measured by PET in the dynamic data-acquisition mode (see Fig. 6). The metabolic half-life of ^{11}C was found to be 70 to 90 min in thigh muscle, which is fairly longer than the physical half-life of ^{11}C.

Measurements of patients treated by a heavy ion beam have also been performed. An image of the deposited activity was obtained for sites of the head and neck, although no clear image was obtained for a treatment site around the lumbar.

5.2. Biology

Biology experiments include: (1) the response of tumor cells to heavy-ion beams, (2) the response of normal tissue to heavy-ion beams, (3) cell damage and the biological effectiveness for various types of radiation, (4) a microscopic study of the cell-killing mechanism, and (5) the biological effects of radiation in the cosmic environment.

5.2.1. LET dependence of RBE values

The biological effectiveness depends on the kinds of radiation: it is known that the linear energy transfer (LET) is the largest factor. Fig. 7 shows cell-survival curves to different LET radiation obtained by using 290 MeV/nucleon carbon beams from HIMAC by Furusawa et al. [5,6].

One of the indices used to measure the biological

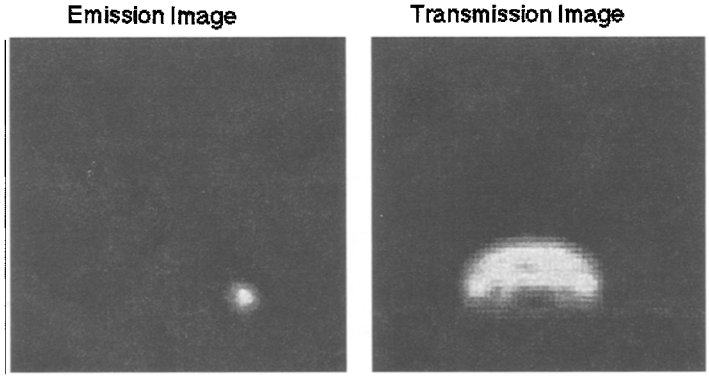

Fig. 6. Obtained image of ^{11}C distribution in a rabbit muscle (left-hand side image). The right-hand figure is a transmission image, corresponding to the whole muscle.

effectiveness is the value of relative biological effectiveness (RBE), which is the ratio of the required dose to obtain the same effect, defined as

$$\mathrm{RBE} = \mathrm{dose(photon)}/\mathrm{dose(tested\ radiation)}.$$

Fig. 8 shows the measured RBE values for various LET values. The RBE values show a maximum at around 120 keV/μm of LET.

5.2.2. Experiments using small animals

Damage to the surface skin is a valuable measure used to evaluate the injury of normal tissue caused by a treatment. Ando et al. [7] studied the effect of fractionation using the skin reaction of mice legs. The relation between the isoeffective dose for skin reaction of 2.5 and the number of fraction is displayed in Fig. 9. The skin reaction is a value which describes the degree of injury. While the total dose increased with the number of fraction in gamma-ray irradiation, the total dose of high LET radiation is less sensitive to the number of fraction.

5.3. Physics and engineering

5.3.1. Truck structure studied with proportional scintillation imaging chambers

The spatial structure of heavy-ion tracks is one of the crucial points for understanding the ion-material interaction. However, a study largely depends on the calculation and speculation in ordinary cases, because the distribution is very tiny.

A new type of detector, a combination of gas scintillation and an image-intensifier-associated CCD camera, was developed by Suzuki et al. [8]. The scintillation light emitted by the filling gas inside the detector was measured by a CCD camera, so that the spatial distribution of the secondary electrons could be visualized. Fig. 10a and b show longitudinal and transverse track images produced by 290 MeV/nucleon carbon ions from HIMAC. These figures give an image of the core and penumbra structure. Since the quality of an image is, in principle, determined by the fluctuation of photon numbers, an improvement of the device is being continued in order to remove induced noise or any effect caused by a non-uniformity of the scintillation.

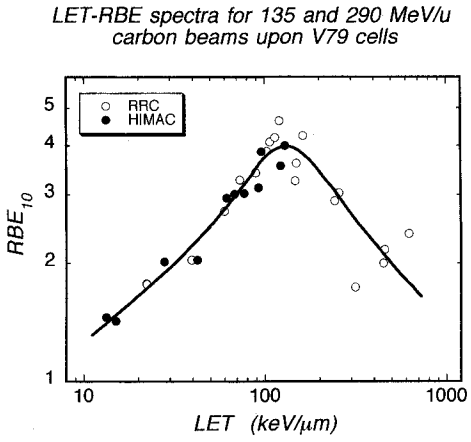

Fig. 8. LET dependence of the measured RBE_{10} values, which is estimated by the 10% survival fraction. Those values were obtained using carbon beams from HIMAC and RIKEN-ring-cyclotron (RRC).

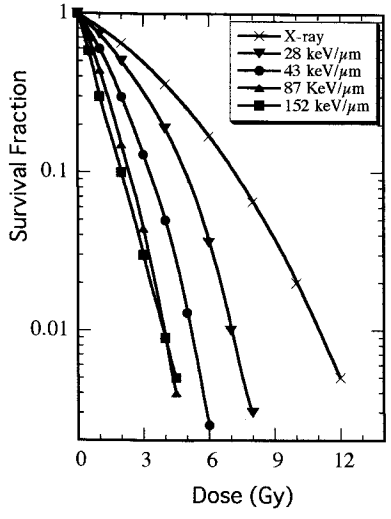

Fig. 7. Cell-survival curves for the radiation of various LET values. Cultured cells of V79 were irradiated by the 290 MeV/nucleon carbon beams from HIMAC. For changing the LET values, Lucite layers with varioius thickness was installed in front of the target.

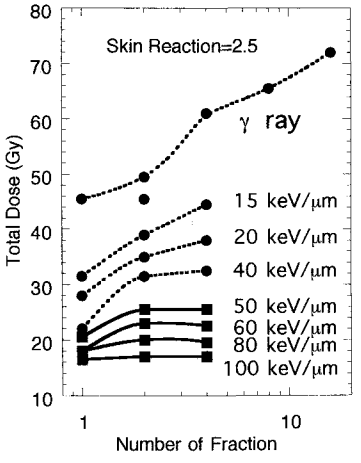

Fig. 9. Isoeffective dose vs. number of fraction for the radiation of various LET values. Irradiation with the same dose were repeated by a number of fraction.

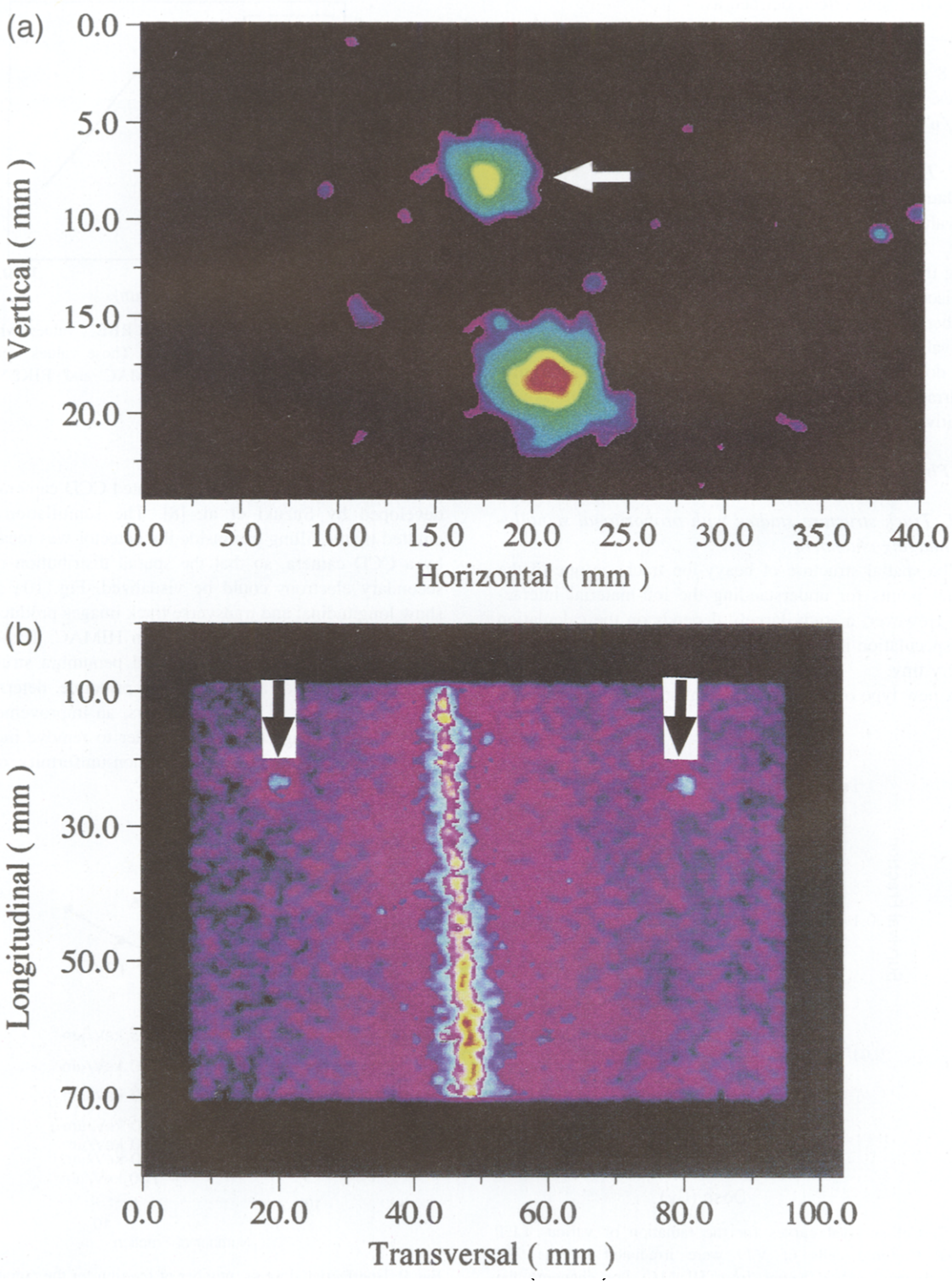

Fig. 10. Observed track structure produced by 290 MeV/nucleon carbon ions. (a) A longitudinal image and (b) a transverse image are shown. Tracks produced by alpha particles, embedded for the calibration, are also shown. (Spots indicated by arrows.)

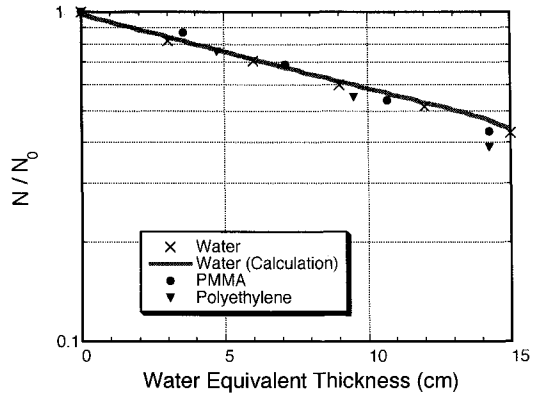

Fig. 11. Attenuation of 400 MeV/nucleon neon beams as a function of the target thickness.

5.3.2. Nuclear fragmentation of heavy-ion beams

The nuclear-fragmentation process is not only of concern for nuclear physics but also for clinical treatments, because a decrease of the primary beams and changing of the depth-dose calculation due to the beam-shaping devices may not be negligible.

Thin plastic detectors placed upstream and downstream of the targets can identify the primary ions passing through the targets. Fig. 11 shows the attenuation of 400 MeV/nucleon neon beams, measured by Fukumura et al. [9], as a function of the target thickness. Several kinds of targets are employed: water, PMMA, and polyethylene, which is commonly used in the beam-shaping devices in heavy-ion treatments. The pulse-height distribution measured by the downstream detector gives a clew concerning the processes occurring inside of the targets. As shown in Fig. 12, many peaks were observed, which were absent without a target. These peaks seem to correspond to ions with different Z values produced by projectile fragmentation.

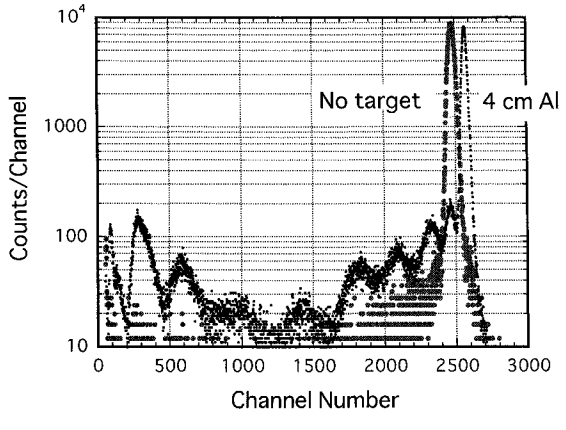

Fig. 12. Pulse-height distribution measured by the downstream detector. The beam of 400 MeV/nucleon irradiated an aluminum target 4 cm thick.

6. Future development

6.1. Time-sharing-acceleration

As described before, HIMAC can deliver beams to three user groups, 'simultaneously', when they use the same ion species. If three kinds of ions can be delivered, the versatility of the facility is greatly increased. To realize this mode, a system of time-sharing-acceleration (TSA) was designed, and is being installed. Three ion sources are being prepared, and most of the magnets of the injector are being replaced by pulse-operated ones. The full TSA mode will be in operation in March, 1998.

6.2. Radioactive-beam course

Fragmentation reactions are the dominant process at the HIMAC beam energies. A new course, which provides radioactive beams produced by fragmentation, is under construction.

One of the possible applications of radioactive beams is to confirm treatment planning by using positron-emitter beams. Since auto-activation requires a large dose, it seems not to be plausibly applied prior to a treatment. Radioactive beams greatly enhance the sensitivity. A detector dedicated to this purpose is being studied.

7. Summary

HIMAC, the medical accelerator facility, has been carrying out clinical studies since 1994. HIMAC is also delivering the heavy-ion beams for research programs in a broad area of basic science. Future developments are progressing to enhance the versatility of the facility.

Acknowledgements

We are very thankful to the operation crew of the Accelerator Engineering Corporation. It should be noted that many researchers both inside and outside of the institute are participating in the research program.

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