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HEAVY ION MEDICAL ACCELERATOR IN NIRS*

F. Soga

Division of Accelerator Physics and Engineering
Research Center of Charged Particle Therapy
National Institute of Radiological Sciences
4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan

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Radiotherapy with use of particle accelerators proceeds in many institutions in the world. Among them the HIMAC project is unique as the first medically dedicated heavy ion machine. The design, construction, characteristics and actual performance are described in detail.

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1. Introduction

Particle accelerator has been developed along with the progress of researches in atomic physics, nuclear physics and particle physics. From the start of nuclear reaction by the Cockcroft Walton with the proton beam of 500 keV in 1932, fundamental research constantly requires higher energy and strong intensity as a main requisite. For long years, variety of different types of accelerators have been invented and developed, leading typically to modern huge colliders. Accelerator technology has realized the stability, high resolution, high intensity, and acceleration of variety of particles such as electron, hadron and heavy ion species.

Recently, apart from the fundamental research for the elementary particle physics and nuclear physics, the applications of the accelerator for technology, industry and other fields became very wide and active. Among them, the application to medical usage of the accelerator becomes remarkably conspicuous and attracts the general attention of the people because it will affect the health of the people and is deeply associated with social welfare.

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2. Radiation therapy with electromagnetic radiation

Nowadays, about 30 % of of the causes for death of the people is coming from the malignant neoplasm; cancer. In Japan, the cancer has been notified as the first position of the cause of the death since 1981. In order to cure these serious patients, there are three different major modalities in general; surgical therapy, chemotherapy and radiotherapy.

Historically, the therapeutic utilization of the radiation was started just after the discovery of X-ray by Roentgen. It was near the end of l9th century (1896) . Since then, long standing usage of the electromagnetic radiations (X-ray and gamma ray) has continued up to now and still most of the radiation therapy is carried out with use of X-ray. Differently from old days of X-ray tubes, most of the X-ray source is produced by the electron accelerators, particularly linear accelerators.

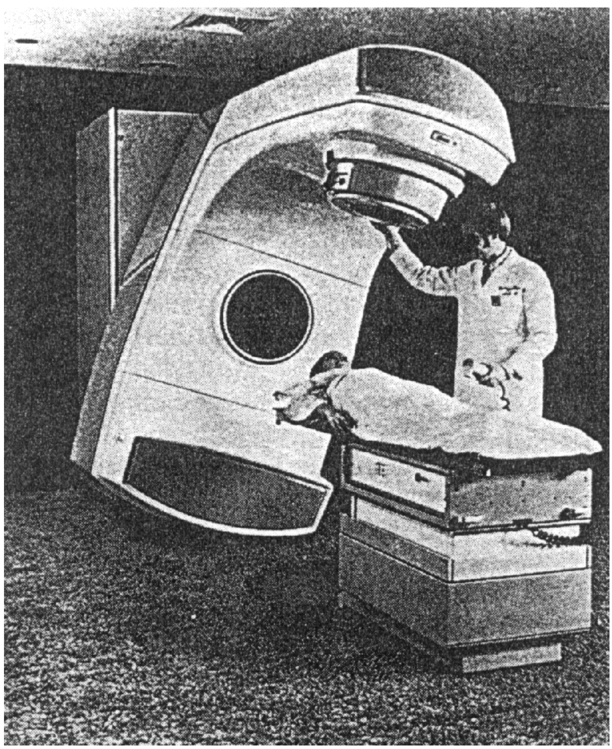

Fig. 1. A photograph of photon therapy with gantry.

Typical irradiation system is seen in the photogragh of figure 1 [1]. A patient lies on the central bed. The ejection of the X-ray is made from the gantry which can be rotated around the patient bed. The inside of the rotatable gantry as an example is shown in figure 2 [1]. Accelerated electrons are bombarded to the metal target, resulting in the continuous spectra of X-ray. The reason why the gantry is rotated is for the sake of concentration of the absorbed dose into the tumor. Otherwise the absorbed dose is much higher in the normal tissue before reaching the tumor part. By the superposition of the irradiation from different directions, it becomes possible to give sufficient dose on tumor without giving intolerable damage on normal part.

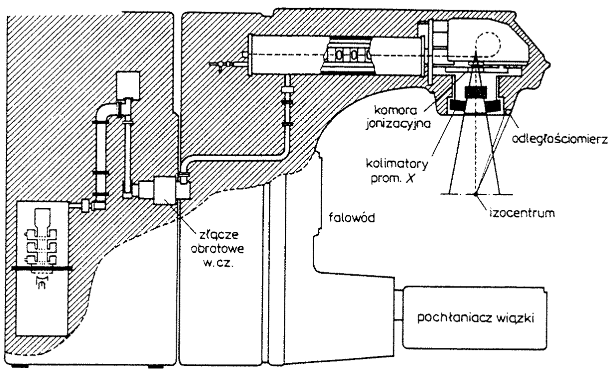

Fig. 2. Typical structure of photon irradiation equipment.

At the exit of ejection it is equipped with multileaf collimator which defines the irradiation toward the cross section from the particular direction and can change the shape of cross sectional collimation. The most advanced technique is Intensity Modulated Radiotherapy (IMRT) which changes the intensity of irradiation associated with changing the direction and collimation. At some institutions, they developed the continuous modulation associated with continuous rotation based on the careful treatment planning owing to the rapid development of computer technology.

3. Neutron therapy

As the neutron has properties of long penetration inside a body and of much larger LET (Linear Energy Transfer) compared to electromagnetic radiation, it has been used for treatment since early times. The first trial was started in U.S.A. with use of cyclotron in 1938 which was 6 years after the discovery of neutron.

In Japan, it was at the National Institute of Radiological Sciences in 1975. The 30 MeV deuteron beam is bombarded on the Be target, and break-up neutrons of 13 MeV in mean energy are used for the treatment. The treatments in NIRS was terminated in 1994, after the treatment of about 2200 cancer patients in various sites. The result of treatments were summarized that compared to the photon treatment, there is not much advantage except in particular sites as salivary gland or other head and neck cancers and caused in some cases more damages resulting in serious late effects. But the 19 year's experience of high LET radiation in treatment in NIRS was worthwhile to provide the planning of next ongoing modality: heavy ion therapy.

Looking at the world, there remains the institutions of neutron therapy. But the number of such places are decreasing. Instead, with accelerators of higher energy, the charged particle therapy as protons and heavy ions are gradually taking the place of neutron therapy.

4. Charged particle therapy

In figure 3 the depth-dose distribution in the human body is shown in case of different radiations. The characteristic curves of the charged particles are completely different from electromagnetic radiation and neutron which have property of exponential damping along the penetration depth. The energy loss curves in proton and heavy ions have rather flat plateau in fast velocity region and sharp peak near the end of their stopping range.

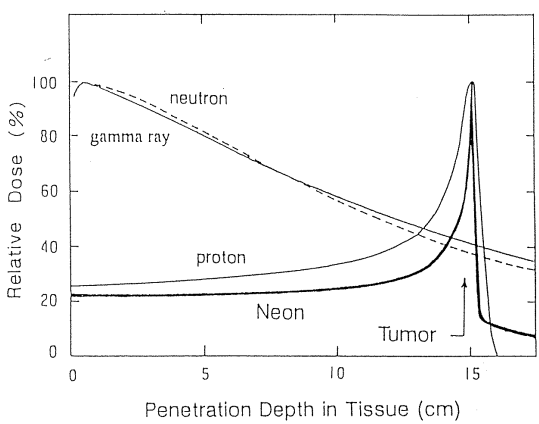

Fig. 3. Depth-dose distributions of various radiations

The advantage of this characteristics for application to radiotherapy was first suggested by Wilson in 1946 [2] . But realization of that proposal had to be waited for certain time. At various institutions in Sweden, U.S.A. and Russia the therapies with use of protons have been conducted since 1957. Among them the Harvard synchrocyclotron has performed treatment of many patients of eye melanoma. The number of the places of proton therapy amounted to more than ten institutions even before 1990, however, most of them are diversion of originally the machines for research of nuclear physics. The first medically dedicated proton accelerator was constructed at Loma Linda University and the treatment of patients was started in 1990 with use of 250 MeV proton beam. On the other hand, utilization of heavy ions to radiotherapy was initiated by using the high energy He beam in 1957, and later they began the treatment with Neon beam of Bevalac at LBL in U.S.A. in 1975 and was continued until the shutdown of that old machine in 1992. The number of patients was 433 in case of Ne beam [3].

During certain time, pion therapies were conducted in the three pion-producing accelerators (Los Alamos, TRIUMF and PSI) . But considering the disadvantage of dose concentration compared to proton and heavy ions, all the pion therapies were stopped by 1994.

5. HIMAC project in Japan

5.1. Design of accelerator

Japanese government launched the policy of "Comprehensive 10 Year Strategy for Cancer Control" in 1983. After the careful study about the ongoing progress of pioneering work in LBL, NIRS decided to construct the medically dedicated accelerator of heavy ions named HIMAC (Heavy Ion Medical Accelerator in Chiba) as a major project of that policy [4]. The design parameters are based on the radiological requirements. Ion species to be accelerated were chosen in the atomic range between He and Ar. He, C, Ne, Si and Ar were chosen as least requirements. The maximum range of the ions in tissue was determined from long clinical experience of conventional radiotherapy in the institute, and range of 30 cm in soft tissue was adopted. Resultant maximum energy of the accelerator turned out to be 800 MeV/amu.

The requirement for dose rate for any ion beam, taking account of some margin was set to be 5 Gy/min which would be sufficient to complete one fractional treatment within 1 minute. The beam intensities for various ions were estimated to fulfil this requirement. The maximum field of irradiation on the tumor of the patients was selected to be 22 cm in diameter. Instead of the rotation gantry like photons or protons, the horizontal and vertical beam transport lines and corresponding irradiation ports were constructed.

The accelerator facility is composed of ion sources (PIG and ECR types), RFQ linear accelerator, Alvarez linear accelerator and two synchrotrons (upper and lower). There are three therapy rooms which are connected to two synchrotrons through variety of beam transport lines. The therapy room A has vertical beam and the therapy room C has horizontal beam port. The therapy room B has both horizontal and vertical beam line ports. Although the horizontal beam is only from lower synchrotron, both synchrotrons can feed the beam to vertical beam ports. Two synchrotrons can be operated simultaneously and independently. The beam pulses from linear accelerators are injected in turn to two synchrotrons by every second, consequently the repetition rate of each beam of synchrotron is 0.5 Hz. Owing to 2 synchrotrons and 2 ion sources (now the 3rd ion source is added) , the recent development of time sharing mode in the accelerator has enabled acceleration of the different final energies and different ion species at the same time, for example, 400 MeV/amu C beam in upper ring and 600/amu Ne beam in lower ring. This technique has made the beam utilization highly efficient and flexible.

5.2. Irradiation facility

In order to use the heavy ion beams for the treatment of patients, it is needed to take various ideas which are particular to irradiation of the beams on the tumor part in the body. Usual spot of the beam from the accelerator is a few or several mm in diameter at the focusing point. The tumors in the patients have generally larger volume in three dimensions. So far, the principle of irradiation on the tumor is to give a sufficient uniform dose throughout the volume to eradicate malignant tumor cells. It is not considered yet to modulate the dose distribution inside the tumor because one cannot find the definite criterion for how to do it. The beam delivery system in the horizontal beam port is shown in Fig. 4.

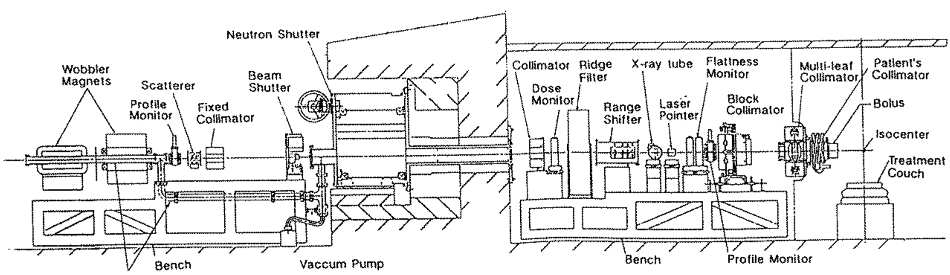

Fig. 4. Layout of the horizontal beam delivery system in irradiation port. System is separated into the area of the beam transport (left) and the therapy room (right) by thick wall.

In order to expand the beam irradiation on the transverse plane, there are generally four methods at present: use of scatterer (one or two) , wobbling method, raster scanning and voxel scanning. In the HIMAC, the combination of a scatterer and a pair of wobbler magnets is adopted. Alternating current magnets of two orthogonal axises are used in association with a scatterer of thin metal foil to form a uniform dose in the lateral distribution. A range shifter uses absorbers to fine tune the ion range to conform the depth of tumor. With use of 10 plastic plates from the 0.25 mm to 128 mm in thickness, their combination can adjust the range of the beam precisely to the depth of the tumor. A ridge filter is an apparatus to spread the narrow Bragg peak. The variety of the ridge filters corresponding to cases for different thickness of tumors in different depths are prepared. Multileaf collimator is a final collimator of the beam before the patient position to tailor the irradiation shape of perpendicular cross-section of the tumor.

The amounts of dose in each fractionated irradiation is a very important quantity. There are two dose monitors, principal and subordinate ionization chambers. These are designed to protect against overdose of radiation in case either counter is disabled. The flatness monitor is comprised of 25 segmented sensitive parts in the ionization chamber. These are to be monitored continuously to keep the uniform distribution of irradiation in the tumor area. All of these devices are operated under computer controls which are set according to treatment planning for individual patients [5].

Before the irradiation, the patient has to be placed as precise as possible on the patient couch with an aid of immobilization devices to fit the treatment planning. Devices for these are laser pointers, X-ray tubes, image intensifiers, and an X-ray CT to confirm the position. Now in HIMAC, less than 1 mm of accuracy of patient position can be achieved in most of the cases by the movement of patient bed.

5.3. Clinical trial

In 1993, the initial investment and construction of HIMAC facility was completed. After about half a year of beam conditioning and preclinical study of physical and biological investigations [6] , the treatment started in June of 1994. The protocols of clinical trial were discussed among many medical doctors in the committees. The head and neck, central nervous system and lung were selected as sites of tumors in the first year. Since then, the numbers of sites have been extended, and by the end of February in 1999, 557 patients have been treated with use of carbon beam. The beam energies from accelerator are 290, 350 and 400 MeV/amu depending on the depth position of tumors in the patients. Various sites and types of cancer have been tried with change of irradiation dose, variation of fractionation, and with variation of numbers or directions of irradiation ports in treatment plannings.

Total numbers of patients until then of different sites are shown in Table I. When the result of treatment is discussed, it is general understanding that in case of cancer one has to wait at least 5 years after the treatment because of the possibility of regrowth of tumor or late metastasis. Thus it is still premature to judge the effect of heavy ion treatments, however, many doctors say that the result of heavy ion irradiation turns out so far remarkably good especially in deep-seated tumors and hard-to-treat tumors by other modalities and in some kind of radioresistant tumors. The heavy ion therapy seems so promising at present that it is to be continued until the definite result may be attained [7].

TABLE I

Number of patients in Heavy Ion Therapy at NIRS from June 1994 to February 1999

Sites	Fy.1994	1995	1996	1997	1998	Sum
Head and Neck	9	10	19	31	22	91
Central Nervous System	6	8	10	6	9	39
Lung	6	11	27	17	28	88
Liver		12	13	19	25	70
Prostate		9	18	10	30	67
Cervical		9	13	11	10	43
Bone and Soft Tissue			9	13	19	41
Esophagous			1	16	4	21
Skull Base				6	4	10
Miscellaneous		24	16	30	17	87
Sum	21	83	126	159	168	557

5.4. Research work

In the HIMAC facility, there are different kinds of experimental rooms in addition to therapy rooms. Those are experimental rooms, for physics and general, for irradiation of biological substances, for utilization of linac beam in medium energy and for use of secondary beams. These experimental rooms have been used primarily for research activity for improvement of treatment method, development of technique of irradiation. One of the fruitful examples is the synchronized irradiation to the respiration of patients which has been actually realized since 1996. In order to minimize the irradiation area in the tumor located in the abdomen, attachment of the sensor for the movement associated with respiration and development of beam extraction from synchrotron by RF knock-out method are combined. Only at the timing of expiration of the patients the beams are irradiated. Now all of the cancer treatments at the sites of lung and liver have been performed by means of this method. Researches on medical physics, radiation physics and radiation chemistry have been pursued. In the biological irradiation room, many different kinds of tissue-cultured cells and small animals are used for study of radiation biology. In the daytime, all the beams are used for treatments, so at night shifts on weekdays and the whole days of weekends they use the beams for these research activities. As for the research works, system is opened not only for domestic members but also for outside people, and now about 400 researchers from outside (including foreigners) are utilizing this facility [8].

5.5. Future development

Heavy Ion Therapy in NIRS is regarded as a project of research work as well as practical treatment, because this modality has a lot of subjects to be further investigated and developed. One of the recent emphasis is the utilization of secondary beams. By irradiation of radioactive beam such as ^{11}C (half life: 20 min.) in the tumor, the irradiation volume will be able to be observed with an aid of positron camera or positron emission tomography (PET) in near future. This kind of beam may become useful for both diagnosis and treatment.

In order to improve the dose localization on the tumor, the development of three dimensionally conformed irradiation method has been investigated. The movement of range shifters is incorporated with that of multileaf collimator to automatically tailor the size and shape of the irradiation field corresponding to the target shape at each depth in a tumor volume of a patient. Another subject is the research for spot scanning method. This technique is especially important in case of weak intensity of the beam such as secondary beam.

There will be many subjects of medical and biological researches : which kind of tumors fit to the heavy ion therapy, what is the mechanism to kill malignant cells or repair the damage, whether there exists any good medicine to be combined with beam irradiation, and so on.

6. Promotion of particle therapy

Now in Japan, one can see a stream of particle radiotherapy projects. The National Cancer Institute at Kashiwa started its clinical study in November of 1998 with use of 235 MeV proton cyclotron facility. In addition, there are 4 projects which are running either under construction or planning funded. In Hyogo prefecture, the construction of the building is over and the heavy ion accelerator is being installed. The composition of the machine resembles to HIMAC with the maximum energy of 320 MeV/amu. In addition, it accelerates protons which will be used for treatments with two rotational gantries. At Tsukuba University, the design of a new medical proton synchrotron is proceeded and already the budget to construct the treatment facility is approved. At Wakasa Bay in Fukui prefecture, they want to extend the present utility for research on industrial technology to radiotherapy. Additional beam course for medical usage is considered. In Shizuoka prefecture, the site of facility is determined and detailed design of linac and synchrotron is proceeded. They want to start treatments in 2002.

When we look at the world, another heavy ion therapy was started at GSI in Germany near the end of 1997. They utilize the beam from heavy ion accelerator (SIS) which has long been operated for fundamental research, for newly built medical irradiation facility. It is said that after experience of some years with present facility, they want to construct medical proper heavy ion accelerator facility.

TABLE II

proposed new facilities for charged particle therapy under construction or planning (January 1999 (Ref. [3] partially revised)).

Institution	Place	Type	1st	Comments
NPTC(Harvard)	U.S.A.	p	1999	235MeV cyclo.; 2 gantries, 3 horiz.
INFN-LNS Catania	Italy	p	1999	70MeV; 1 room, fixed horiz. beam
Hyogo	Japan	p, ion	2001	230MeV p, 320MeV/n ion synchro. 2 gantries, 2 horiz. 1 vert., 1 45 deg beam
NAC, Faure	South Africa	p	2001	200MeV cyclo. new beam line 30 deg
Tsukuba	Japan	p	2001	270MeV synchro, 2 gantries; 1 horiz. 1 research room
CGMH	Taiwan	p	2001?	250MeV syn. or 235MeV cyclo. 3 gantries, 1 fixed
Wakasa Bay	Japan	ion	2002	200MeV p; 1 horiz. 1 vert. Tandem + synchro. multipurpose
Bratislava	Slovakia	p, ion	2003	72MeV cyclo. p, ions, BNCT, isot. prod.
Shizuoka	Japan	p	2002	250MeV synchro. 2 gantries, 1 horiz.
Erlangen	Germany	p	2002?	4 treatment rooms, some with gantries
CNAO, Milan Pavia	Italy	p, ion	2004	synchro. 2 gantries, 1 fixed, 1 exp. room
Heidelberg	Germany	ion	2004?	430 MeV/n synchro.; 2 gantries, 1 horiz.
AUSTRON	Austria	p, ion	?	2p gantry; 1 ion gantry, l fixed p, 1 fixed ion
Lyons	France	ion	?	?

There are many places where new medical facilities of proton or/and heavy ion beams are expected. In Table II, those projects are listed either under construction or in design phase. In due course, a lots of serious patients of cancer will be treated and cured with particle therapies in many countries.

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