

Progress of Heavy Ion Therapy

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1. Introduction

The charged particle therapy has currently two kinds, either proton therapy or carbon ion therapy. So far, two accelerator facilities in the world have been conducting heavy ion therapy using carbon beam. The first is the HIMAC at the National Institute of Radiological Sciences in Chiba, Japan. The construction of medical accelerator was decided in 1983 along the policy of the government "Comprehensive 10 Year Strategy for Cancer Control". The discussion and decision were based on the pioneering work of treatment trial made with the Bevalac at the Lawrence Berkeley Laboratory with use of neon beam starting from 1975. They tried about 400 patients, but Bevalac was shut down in 1992; the facility was old. HIMAC started its clinical trial in June of 1994.

The other place, where the heavy ion therapy has been done, is the SIS facility at GSI in Darmstadt, Germany. Originally this machine is for research of fundamental physics and its applied sciences; the operation of the machine began at the early time of 1990's. After addition of a treatment room in the experimental area, they began the heavy ion treatment in December of 1997. Both facilities are composed of similar combination of elements: ion source, linear accelerator and synchrotron. The energy of the heavy ions has to be several hundreds MeV per nucleon so that the beam may reach the tumor position inside the human body. This need results in the use of synchrotron as the main machine in the accelerator complex.

2. Characteristics of Heavy Ions for Radiotherapy

What are the characteristics of heavy ion for radiotherapy? Compared to conventional radiotherapy with x-ray or gamma ray, they have several strong advantages. These are listed below in the Table 1.

Table 1. Characteristics of Heavy Ions for Radiotherapy

1. Excellent Dose Distribution
2. High LET gives High RBE(Relative Biological Effectiveness)
3. Smaller Dependence of Oxygen Concentration
4. Reduction of Cell Repair
5. Less Variation in Sensitivity on Cell Cycle

The strongest one is the physical factor, that is, excellent dose distribution. The Figure 1 shows the example of comparison. The malignant tumor is located in the center. The spinal cord is highly sensitive to radiation and it is desirable to avoid the irradiation on that part. When the tumor is irradiated either x ray or carbon ion from two orthogonal directions, in case of x ray, the normal portions accept high dose, in particular, near the surface, and also some part of spinal cord receives the radiation. In contrast, the carbon beam has the much better dose distribution. With use of bolus, irradiation to spinal cord can be completely avoided.

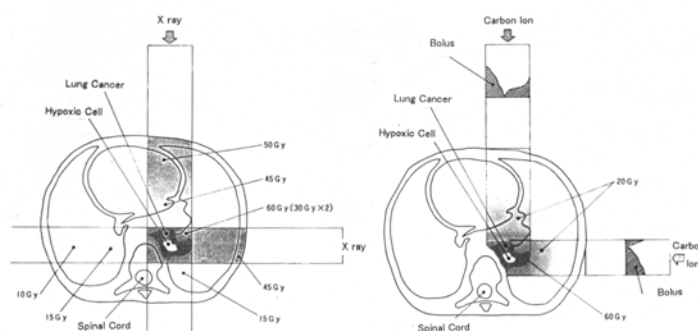


Fig. 1. The comparison between x ray and carbon beam irradiation

Other strong characteristics are related to biological factors. Among 4 factors in the Table 1, the RBE and OER(Oxygen Enhancement Ratio) are highly important ones. These biological effects are 2 or 3 times as strong as the other photon radiation in the same physical dose. In this respect, the RBE and OER of the proton are similar to photon, though it has also the sharp distribution. This is the main difference between proton and heavy ions.

3. Proceeding of the Heavy ion Therapy

When we started a design of accelerator facility, the first consideration was medical requirements coming from long experience of photon and neutron therapy in our institute. These are listed at left side in Table 2. Since it was not determined yet the appropriate ion species for therapy, there were wide variation of candidates for acceleration. Other items were range of penetration, dose rate including certain margin, area of irradiation field and so on.

Table 2. Medical Requirements and Accelerator Specification

Particle Species	He to Ar	Ions	He, C, Ne, Si, Ar
Penetrating Range	30 cm in Tissue	Max. Energy	800 MeV/n
Dose Rate	5 Gy / min.	Min. Energy	100 MeV/n
Maximum Field	22 cm in diameter	Beam Intensity	$2 \cdot 10^9$ pps/ring(C)
Beam Direction	Vertical & Horizontal	Repetition Rate	0.5 Hz/ring

In order to satisfy the above conditions, accelerator specifications were set at right side. It is composed of the ion sources, RFQ linac, Alvarez linac, and 2 synchrotrons. There are 3 therapy rooms: one for vertical beam, one for horizontal beam and one for both beam directions. Besides several experimental rooms are prepared for physics and biology.

We have set up the open utilization system for domestic and outside users which exceed now over 120 groups including not only medical related studies but also research works of any kind which use the heavy ion beam. At present, about 40 foreign scientists are joining the research activities, which are conducted at nights and week end.

The main difference between NIRS and GSI lies in their irradiation systems. At the HIMAC, the beam is broadened with wobbler magnets and scatterer. We chose a conservative method as the same as preceding Bevalac. In order to measure the dose, there are two monitors for safety, parallel ionization chamber and secondary emission monitor. Multileaf collimator having 23 thin steps of stacked leaves at both sides can be moved to make the beam path matched to the transverse cross section of the tumor. The thickness of each leaf is 6.5 mm. In case of small tumors, the brass collimator are manufactured. Bolus made of acryl for range compensator is provided for each portal irradiation .

In the GSI, they are using a spot scanning method. All the magnets in the transport line are made of alternate current type so that they can follow the change of beam energy instantaneously. Consequently, they do not use the ridge filter, collimator, nor range shifter. According to the latest news from "Particles"¹, GSI has gradually accumulated the experience of patient treatments though it is not the medical proper machine. The total number of patients treated there is 84 during 3 years and a half at the date of June this year.

The Table 3 shows the number of patients at the NIRS by the time of August 2001. Seven years ago when it started, it was small, but now about 200 patients can be treated every year.

Table 3. The Number of Patients at the NIRS from June 1994 to August 2001

Head & Neck	178	Bone & Soft Tissue	91
Centr.Nerv.System	65	Esophagous	23
Lung	187	Skull Base	16
Liver	119	Pancreas (prior to ope.)	6
Prostate	144	Rectum (recurrence)	2
Uterine Cervix	69	Eye(melanoma)	4
		Miscellaneous	138

The sites of treatment have been gradually extended. Last year, they started the treatment of one of the most hard to treat cancer, pancreas. Now the total number of patients treated is over one thousand.

Table 4 is the overall local control rate in HIMAC. There is a lot of systematic study along the treatment protocols with variation. The scores are listed for 12, 24 and 36 months after the treatments. Score varies site by site, but according to medical doctors, in many cases, unexpectedly good results are coming out. Compared to statistics of last year, certainly the average numbers of control rate are upward. As for the protocol, for example, the fractionation in liver cancer is reduced from starting 15 times to now only 4 times.

Table 4. Overall Local Control Rate in the HIMAC treatment

	12 months	24 months	36 months
Statistics in Aug. 2000	82.0 %	67.1 %	56.9 %
Statistics in Aug. 2001	83.8 %	69.1 %	62.5 %

4. Advancement in Irradiation Method

While the treatment continues in the HIMAC, there are developments of research both in accelerator engineering and irradiation technique in our department.

4-1. Synchronized Irradiation with the Respiration of the patients

Some organs are moving along with the breathing during the irradiation. In order to minimize the irradiation on normal part, synchronized irradiation with respiration of the patients was developed particularly in case of targets such as lung, liver tumors. This method required two different progresses. One concerns the accelerator and the other the irradiation side.

Usually for treatment, the beam is slowly extracted from the synchrotron with a third integer resonance, because the control of dose at each time of irradiation must be within a few %. Actually in HIMAC, this accuracy is usually below 1 %. For synchronized irradiation with respiration, the extraction and shut off of the beam should be done much more rapidly as well as irregularly. The accelerator group developed an Radio-Frequency Knockout method which use the beam heating by a transversal RF field for the circulating beam in the synchrotron leading to rapid switching of the beam. At the same time, the basic extraction time from synchrotron is elongated to the beam duration of 1.5 seconds with duty factor 50 %.

The other technique is the production of electric signal gate associated to the movement of abdomen due to the respiration of the patient. This is made with use of the infrared light-emitting diode attached to the patient's body and position sensitive camera. This system generates the gate for request a beam around the end of the expiratory phase. These two techniques are combined and it has been realized in actual treatment since 1996².

4-2. Broad Beam Three Dimensional Irradiation Method

The present method of Spread Out Bragg Peak by using wobblers magnets and scatterer has a certain small disadvantage. Though there is a sharp cut off at the distal edge with use of bolus, there is an excess dose for normal tissue around the

proximal region. This unwanted dose should be reduced to smaller level. In order to improve such distribution, it is necessary to combine the dynamic movements of range shifter and multileaf collimator. This is the long-standing subject and finally this technique will be realized within this year. Though the hardware was provided fairly in early days, it takes long until the difficulty of setting up for the treatment planning which is related to dose control for each thin slice is resolved so as to obtain optimal distribution.

4-3. Utilization of Secondary Beam for Confirmation of the Range of the Irradiated Position and Area, and associated Spot Scanning Method

This is also an important long-standing subject, as we know the unique and promising possibility of heavy ion beams from the beginning. A plan is to use ^{11}C which has a half life of 20 minutes. Its production rate of intensity is 0.4 % of the primary beam of ^{12}C .

In order to use the faint and precious quantity of secondary beams, the spot scanning system has been developed³. In the wobbler & scatterer system, the effectively used particle numbers for patient is 20 -25 % of total beam flux. In an irradiated area of within 10cm \times 10 cm, a spot scanning system can make use of total flux of the secondary beam owing to RF-knockout extraction method. We are now successful to get the biological flat dose distributions in the longitudinal and transverse direction at the test dose of 2 Gray and these are illustrated in Figure 2.

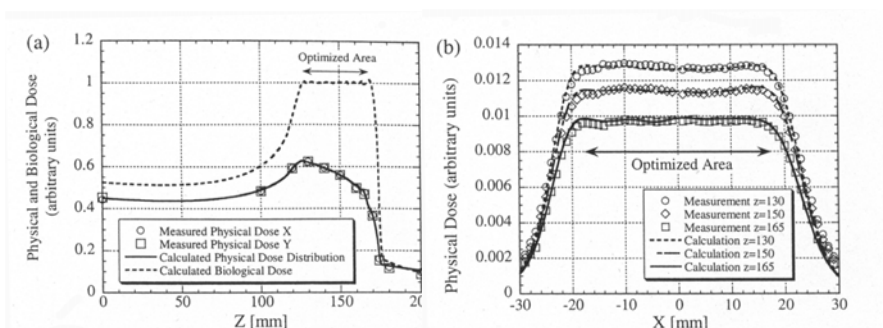


Fig. 2. Longitudinal and transverse dose distributions in spot scanning

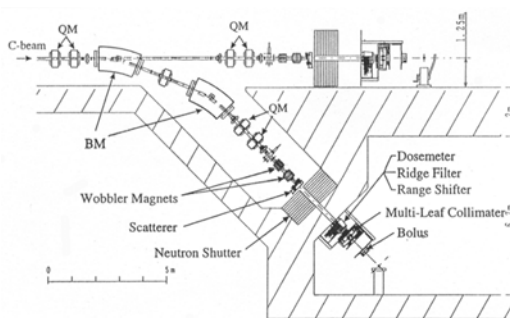
The first irradiation for the patient at least for confirmation of range of the particles, will be started next year, and it is hoped that eventually some of the treatment itself will be done with radioactive beam.

5. Towards Propagation of Heavy Ion Therapy

In order to prevail this modality in the society, it is required to make more efforts to get an idea of small-sized accelerator and develop more efficient treatment system.

In our institute, the project of research and development of elements in accelerator toward smaller scale has started this year. It is the design of smaller

Fig.4.
Beam Transport
Line and
Irradiation
System



ring for that purpose. Though the energy is rather low, various smaller elements in synchrotron and novel technique will be pursued and tested. We believe at present that for heavy ion therapy, it is not suitable to use the gantry, because it is strong advantage of heavy ion therapy that even without gantry the very excellent result is coming out, and besides the gantry required big cost for construction.

In order to manage the reasonable cost in routine operation, the handling capacity for number of daily patients is an important factor. Looking at the fact that most of the time is spent for the precise positioning of the patient on the bed or chair, it is desirable that, before the patient is placed at the irradiation place, the fixation of the patient is already done on the bed or chair. Probably the variation of consideration of this kind remains quite a lot and helps the heavy ion therapy to expand more and more in the society and people will receive the larger benefit in the future.

As a conclusion, I would like to say that, the Heavy Ion Therapy results certainly in the very promising modality. It is very important issue to consider how to promote and prevail this excellent scientific technology in the society.

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