FAST NEUTRONS AND PROTONS IN CANCER TREATMENT WITH THE MEDICAL CYCLOTRON AT NIRS

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SUMMERY

Radiation therapy has made marked progress following introduction of high energy x-ray, gamma ray and electron accelerators. Nevertheless, the fact that the doses delivered to the target volume depend on radiation tolerance of the normal tissues still remaims critical problems.

At National Institute of Radiological Sciences (NIRS), medical cyclotron was installed on 1973 and the clinical trials with 30 MeV d-Be neutrons initiated on 1975.

The results of clinical trials with fast neutrons show that the patients suffering from locally advanced cancers and radioresistant cancers achieved local control of the tumor under radiation tolerance of the normal tissues. The Pancoast tumor of the lung and osteosarcoma found to be the typical indication for fast neutron irradiation.

Clinical trials with 70 MeV protons for the patients suffering from superficial cancers started on 1979, because the beams are able to penetrate only 36 mm depth of the normal tissues. The results show that the tumors were controlled without complications of the normal tissues, excluding the patients who had the tumors recurred after radical irradiation. For the patients with malignant melanoma, salvage surgery was necessary to manage the residual tumors.

Based on the experiences of clinical trials with fast neutrons and protons, project studies using accelerated heavy ions, characterized by Bragg peak and high LET, have been organized at NIRS in 1984.

Clinical trials with heavy ions will start within 10 years.

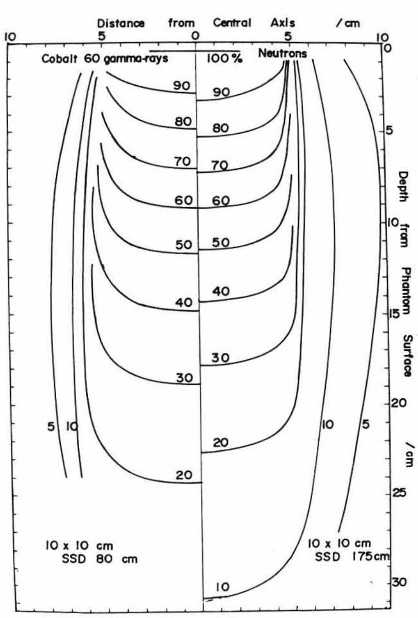

Fig. 1 Dose distributions for 30 MeV d-Be neutrons (NIRS)

INTRODUCTION

Radiation therapy has made marked progress following introduction of high energy x-ray, gamma ray and electron accelerators. Nevertheless, the fact that the doses delivered to the target volume depend on radiation tolerance of the normal tissues still remains critical problems.

In Japan, the patients refered to radiation therapy consisted of 40 % of all patients suffering from malignant diseases and a half of whom received radiation therapy developed local recurrence.

To reduce the rate of recurrence, the studies have been performed to improve dose localization at the target volume and to enhance the effect of radiations on the tumor cells.

At National Institute of Radiological Sciences, medical cyclotron was introduced to evaluate the biological effects of high LET radiations on the tumor cells and to confirm the relationship between dose localization and local control of the tumor.

Results of clinical trials with fast neutrons and protons are evaluated and future plans for use of Heavy Ion Medical Accelerator are discussed.

FAST NEURON THERAPY

Fast neutrtons produced by bombarding a thick Beryllium target with 2.8 MeV deuterons accelerated by a van de Graaff generator were used for preliminary clinical trials. Thirty-six patients who were suffering from superficial cancres participated to the clinical trials between 1969 and 1975, because of low penetration of the beam. The results showed that 8 of 12 patients who had malignant melanoma achieved local control of the tumor and that 2 of 3 patients who were suffering from soft tissue sarcoma

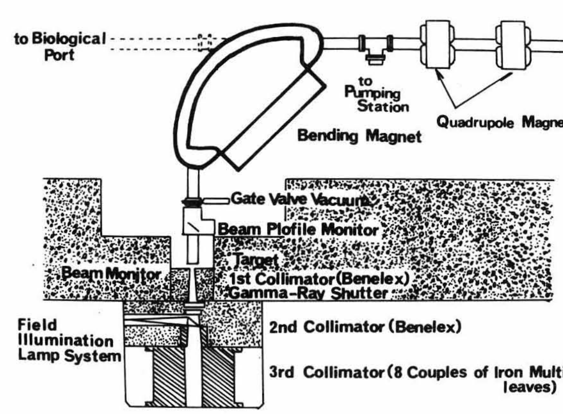

Fig. 2 Schematic diagram of the system for 30 MeV d-Be neutrons (NIRS)

had local control of the tumor. Since the results of clinical trials with low energy fast neutrons were excellent to control of the radioresistant cancers, the studies have been advanced to use high energy neurtons , which were produced by the medical cyclotron installed at National Institute of Radiological Sciences. The clinical trials with 30 MeV d-Be neutrons started on November 1975.

1. Physical Characteristics of the Beam :

The fast neutron beams were produced by bombarding a thick Beryllium target with 30 MeV deuterons. The vertical neutron beamms are collimated by a hydrogen rich material, Benelex,which was supplemented by an additional steal collimator. By adjusting the latter, irregular fields can be conformed according to the tumor margine. The dose distributions of the fast neutron beam measured in 10 x 10 cm field at SSD 175 cm and those of Tele-Cobalt gamma rays obtained in 10 x 10 cm field at SSD 80 cm are shown Fig. 1. The fast neutron beams make muximum build-up of the dose at 6 mm below from the surface. The depth dose curves for fast neutrons and for gamma rays reach 50 % dose level at 11.9 cm in the tissue equivalent phantom.

The dose rate in the tissue equivalent phantom was 42 rad (n, γ) per 30 A for 11.4 x 11.4 cm field at SSD 200 cm. Gamma-ray contamination was estimated to be less than 4 % of the beam.

2. Biological Effects :

Biological effects of fast neutrons are characterized by high energy transfer to the tissues and tumors.

Recoiling protons, which are produced by the results of interaction between fast neutrons and the nucleus of hydrogen, transfer high linear energy to the tissues.

Physical studies show that dose average LET was found to be 50.9 KeV / for 30 MeV d-Be neutrons.

The features of biological effects of fast neutrons compared with photon beams are summerized as follows.

a. Low oxygen enhancement ratio.
b. Low repair capability of the irradiated cells.
c. Low fluctuation of radiosensitivity in the cell cycle.

The results of experiments performed in various biological systems confirmed the facts that the biological effectiveness of fast neurtrons relative to photon beams found to be high and the RBE values were usually enhanced, when the evaluation was performed on the late effects of the normal tissues. The results also suggest that as the number of fractions increased RBE values for fast neutrons become higher compared with those obtained in the single dose irradiation (Table 1).

Since the radiosensitivity of the spinal cord to fast neutrons is high compared with soft tissues, the cord has to be protected during irradiation in order to prevent paresis of the extremities. The radiation tolerance of the spinal cord was reported to be 8.5 Gy for 16 MeV d-Be neutrons (Hornsey, S.).

Slowly growing tumors, such as carcinoma of the salivery gland, have shown good response to fast neutron irradiation (Battermann, J.J.).

Hence, it is suggested that fast neutron beams have to be used under the conditions, where the depth doses of the beam should be equivalent to those of high energy x-rays, and the target volume has to be made as small as possible.

3. Clinical Trials :

There were 1,400 patients suffering from either locally advanced cancers or radioresistant cancers treated with fast neutrons between 1975 and 1986. The patients refered to National Institute of Radiological Sciences when the cyclotron was under operation were treated with fast neutrons, whereas the patients visited when the accelerator was under scheduled maintenance received photon beam irradiation. The modalities for fast neutron therapy consisted of three schedules ; i.e. fast neutron only, mixed schedule and fast neutron boost. When the mixed schedule was prescribed, fast neutron beams were irradiated in every Monday and Friday, and the remaining 3 days between them were reserved for photon beam irradiation. In the case of fast neutron boost, 40 Gy of photon beams were followed by neutron irradiation to the target volume when the tumors seemed to be radioresistant. When the radical treatment was scheduled, the patients received total doses equivalent to TDF (Time dose and fractionation factor) 100 - 120 to the target volume.

Table 2 shows local control rates of the tumors treated with either fast neutrons or photons, where evaluation was performed for all stages of the tumors. The results show that when fast neutrons were used the patients achieved local control of the tumor in higher rates in the treatment of carcinoma of the larynx, esophagus and osteosarcoma, compared with the rates obtained by photon beam irradiaiton.

Improvement of local control of the tumor were confirmed in the treatment with fast neutrons for carcinoma of the lung and prostate gland, and soft tissue

Table 1 RBE values of Late Effect of the Normal Tissues for Fast Neutrons

	Neutrons	Tissues	RBE	Type of Fractions
Withers, H.R	50 MeV d-Be	Skin (Pig)	3.94 3.11	5 fraction / wks
Hornsy, S.	7.5 MeV	Lung (Mice)	1.45 + 0.14	Single dose (1200 rad)
Zook, B.C.	15 MeV	Pancreas(Beagle)	3.0 - 4.5	4 fractions/w/6 wks
Stephens, L.C.	50 MeV d-Be	Cord (Monkey)	4.2 - 4.6	270 rad x 9 fractions / 29 days
Hopewell, J.W.	42 MeV d-Be	Skin (Pig)	1.5	Single dose
		Kidney (Pig)	2.0	Single dose
Hussey, D.H.	50 MeV	Oral cavity(Monkey)		Photon fraction size
			3.0	200 rad
			2.5	400 rad
		Nephritis(Monkey)	2.5 - 2.8	340 rad
van der Kogel,A.J.	15 MeV d-T	Cord (Rat)		2 fraction (Photon dose)
		Lumbar	1.6	1650 rad
		Cervical	2.0	1370 rad

sarcoma.

The patients suffering from malignant melanoma achieved excellent local control of the tumor, where pre-operative irradiation was provided with fast neurtrons.

Of 54 patients suffering from carcinoma of the uterine cervix, Stage III, 39 achieved local control of the tumor (72.2 %) in the treatment with fast neutrons, whereas the rate was 64.8 % (35 / 54) in the photon beam series. Unfortunately, there was no significant differences in 5 year survival rates between the series of fast neutrons and of photon beams. The reasons might be explained by the fact that, for locally advanced carcinoma of the uterine cervix, the survival rates of the patients strongly depend on the incidence of metastasis in the para-aortic lymph nodes.

Table 2 Local Control Rates of Cancers treated with either Fast Neutrons or Photons

Site of Cancers	Local Control Rates	
	Neutrons	Photons
Larynx	48.3% (15/31)	39.0% (84/214)
Lung	46.9% (38/81)	
Esophagus	44.1% (15/34)	29.6% (24/81)
Uterine Cervix	72.2% (39/54)	64.8% (35/54)
Prostate Gland	94.0% (17/19)	
Soft tissue Sa.	70.6% (48/68)	
Osteosarcoma	59.3% (19/32)	35.3% (6/17)
Malignant Melanoma	80.0% (17/21)*	

* The cases with preoperative irradiation

a. Carcinoma of the Larynx : In the treatment of the patients suffering from carcinoma of the larynx, fast neutrons were boosted to the target volume following irradiation with 40 Gy of x-rays. Of 13 patients suffering from suprs-glottic cancer of the larynx, 11 have had local control of the tumor (84 %), whereas local control of the tumor was seen in 25 of 100 patients (25 %) who received photon beam irradiation only (Table 3).

The results were almost even in the cases suffered from glottic and sub-glottic cancers treated with either neutrons and photons.

Salvage surgery was necessary to manage carcinoma of the hypopharynx, because local control of the tumor was observed in only 3 of 6 patients after neutron therapy.

b. Lung Cancer : Fast neutron irradiation were prescribed for 21 patients suffering from Pancoast tumor of the lung between 1976 and 1984, 11 of whom had the disease of Stage III and the other had Stage IV cancers.

The results show that 5 year cumulative survival rates for all patients was 32.2 % and 10.0 % for the patients with Stage III and IV disease respectively. Whereas, no patients were surviving at 5 years when the patients received the treatment with either surgery alone or photon beam irradiation.

Of 7 patients who were suffering from adenocarcinoma of the lung, Stage I, and were treated by fast neutron irradiation, 4 were surviving at December 1985 without late damage. The cumulative survival rate for them was 52 %.

Table 3 Local Control Rates of Carcinoma of the Larynx treated with either Fast Neutron Boost or Photons (Cancer Research Institute Hospital)

	T1	T2	T3	T4
Glottic	3/5 (48/57)	5/8 (8/19)	0/2 (3/27)	0/1 (0/1)
Supra-glottic	2/2 (4/8)	3/3 (12/34)	4/6 (7/31)	2/2 (2/27)
Sub-glottic		1/1 (0/5)	0/1 (0/5)	

( ) : Photons, 1964 - 1971

This results show that, when fast neutron beam was used in the limited field size and was irradiated to the target volume only, the merit of high LET radiation was expected on the tumor control without late radiation damage of the lung tissue.

c. Osteosarcoma : The patients suffering from osteosarcoma have been treated with multi-modal basis, because the tumors are markedly radioresistant and the incidence of remote metastasis is high. Hence, chemotherapy is prescribed in various combinations of the drugs during radiation therapy and at the follow-up studies.

At the beginning of the treatment, the doses of fast neutrons equivalent to TDF 120 were delivered to the target volume in order to evaluate the response of the tumor and the damage of the normal tissues. After confirmation of the effects of fast neutrons on the tumor and on the normal tissues, the aim of the clinical trials was placed on preservation of the function of the leg. Finally, the decision was made to use the doses equivalent to TDF 80, which were found to be optimal to performe prosthesis without late radiation damage of the soft tissues. When the disease was advanced, amputation of the leg was necessary, because the merit for prosthesis could not be expected.

between 1976 and 1984, 54 patients suffering from osteosarcoma were treated with fast neutrons. For 44 patients of whom received radical radiotherapy, cumulative 5 year survival rate was 67 %, whereas the rate was 19 % for the patients received photon beam irradiation.

When the evaluation was done in 20 patients who received limb salvage operation, the cumulative 5 year survival rate was 85 %.(Fig. 3).

On the other hand, the data of the follow-up studies show that late damage of the skin was almost even between the series who received either fast neutron beams or photon beams.

Table 4 Results of Clinical Trials with Fast Neutrons for the Patients suffering from Pancoast Tumor of the Lung (1976 - 1984, NIRS)

Stage	Number of Patients	Age (Mean)	TDF (Mean)	Dead	Mean Survival Months	Cumulative 5 Year Survival Rate
III	11	62	116	8	21.2	36.3 %
IV	10	62.6	107	9	8.7	10.0 %
Total	21	62.2	112	17	14.6	23.2 %

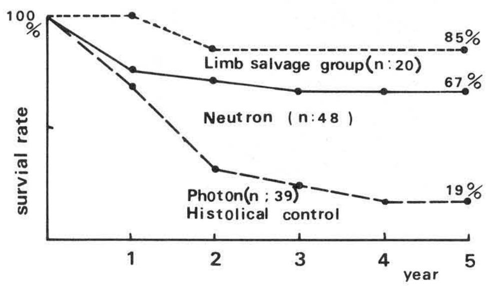

Fig. 3 Survival Rates of the Patients suffering from Osteosarcoma treated with either Fast Neutrons or Photons (Takada, N.)

PROTON THERAPY

Protons lose the energy mainly by interaction with the electrons orbiting around the nucleus of the tissue and make Bragg peak.

Since the beam range is limited and side scattering is less than photon beams, the tumor volume at any depth can be irradiated without excess exposure to the surrounding normal tissues.

However, the results of the experiments with proton beams have not shown the biological effects observed in high LET radiations on the normal tissues and tumors, because the energy transfered by recoil nucleus at the end of the beam range found to be low compared with neutrons and disseminated when the Bragg peak is spread out. Therefore, the aim of the clinical studies with protons was placed on evaluation of the excellent dose localization in tumor control.

1. Protons and Physical Arrangement of the Beam :

Clinical trials with 70 Mev protons started on October 1979 at NIRS. The proton beams used make Bragg peak at 36 mm depth in the phantom (Fig. 4).

To develop the technique for proton therapy and to establish clinical trials, a new beam line have been constructed in the physical experimental room of the cyclotron building. The beam line consists of three monitering chambers, two sets of beam shaping slits, a beam shutter, and two orthogonal bending magnets (Fig. 5).

The power suplies of these bending magnets are digitally controlled by minicomputer and the 10 mm^2 spot beam of protons can be directed by these magnets to any points within a 20-mm^2 radiation field. This two-dimentional spot beam scanning system has made it possible to achieve an irradiation field of any irregular shape and intensity distribution to correct fluctuation in the beam density. An example of the irradiation field of protons controlled by the spot-beam-scanning system is shown in Fig. 6, where the beams skipped at the vulnerable area and made hot spots within the target.

After confirmation of the two dimentional spot-beam -scanning system, the studies have advanced to develop three dimentional beam-scanning system.

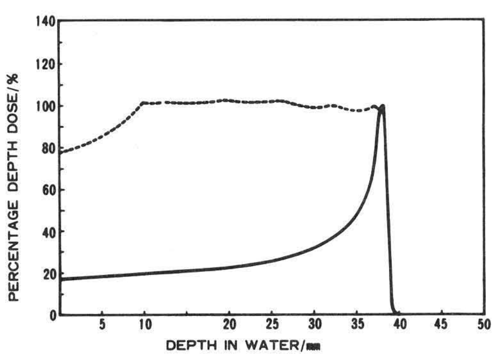

Fig. 4 Dose Distributions of 70 MeV Protons, Primary and Extended Beam (Hiraoka, T.)

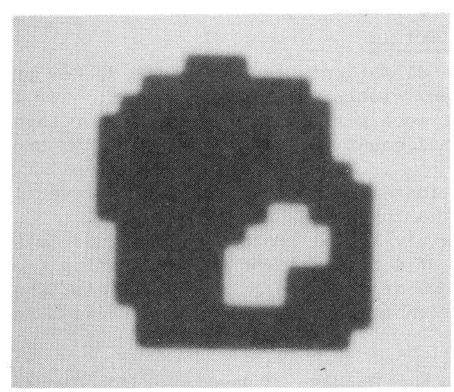

Fig. 6 An Example of the Irradiation Field of 70 MeV Protons obtained by Spot-Beam-Scanning System (Kanai, T.)

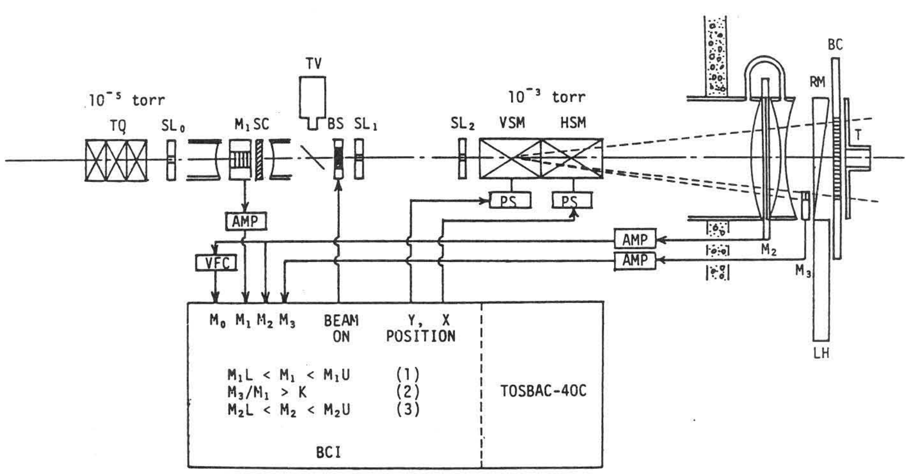

Fig. 5 Schematic Diagram of the Spot Scanning System for Proton Beam (Kanai, T.)

The experimental results showed fairly good agreement berween the planned and the measured isodose distributions (Fig.7, 8).

These results indicate that the three-dimentional spot-beam-scanning method for proton conformation radiotherapy was effective for reducing the dose to the normal tissues compared with the two-dimentional spot-beam-scanning or the broad beam irradiation. This irradiation system will probably usefull for heavy charged-particle radiotherpy in the future.

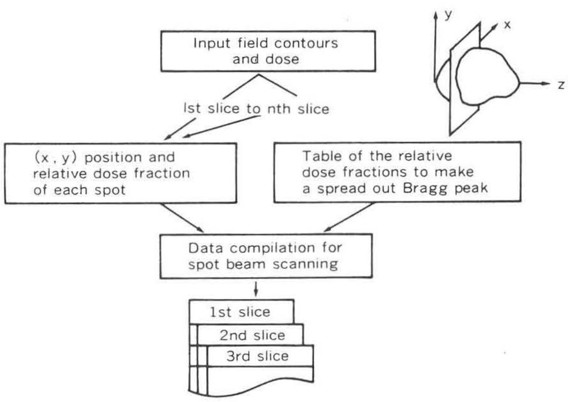

Fig. 7 Schematic Diagram for Three-Dimentional Spot-Beam- Scanning System for Protons (Kanai, T.)

2. Clinical Trials :

Ther were 41 patients treated with 70 MeV proton beams between October 1979 and June 1986. Of 41 patients, 31 were suffering from cancers or sarcomas, and 10 had malignant melanoma, of whom 6 had choroidal melanoam.

of 22 patients who had cancers, 17 achieved local control of the tumor (82 %) (Table 5).

Unfortunately, local control of the tumor was only seen in one of 4 patients who were suffering from malignant melanoma of the skin. Of 6 patients, who had choroidal melanoma, 3 were getting sufficient responce

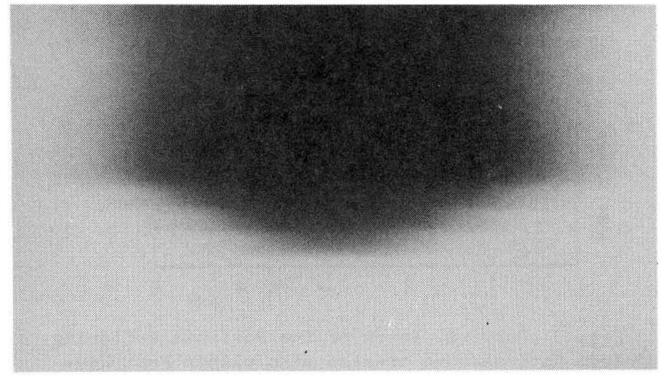

Fig. 8 Radiogram of Protons obtained by Spot-Beam-Scanning System illustraing in Fig. 7.

to proton irradiation (Table 6).

There were 5 patients who developed late complications following proton irradiation. Three of 5 patients had the tumors recurred after radical radiotherapy and refered to proton therapy.

It was confirmed from the results of clinical trials with protons that, when the radiations with excellent dose distributions were used, the patients could achieve local control of the tumor with reduced complication rates compared with photon beam therapy.

DISCUSSION

Fast neutron therapy was introduced for cancer treatment in 1938 by Dr. Stone, and was discontinued in 1942, when 250 patients participated to the clinical trials firstly organized. The reasons why the clinical trials were discontinued were explained by the facts that the biological effects of the fast neutron beams have not been fully examined, and that the late effects of the normal tissues within the field of irradiation were severer than those expected befor treatment.

After the 2nd World War, clinical trials with fast neutrons were conducted at Hammersmith Hospital, London, in 1968, based on the results of biological studies for high LET radiations in tumor control, which were effective to cure radioresistant tumors, i.e., malignant

Table 5 Results of Treatment for Cancers with Protons (70 MeV) : NIRS (1979 - 1986)

Sites	Cases	Local Control: Protons Only	Local Control: Salvage Surgery	Complications
Skin	5	4	-	-
Breast (Local recurrence)	7	7	-	3 1)
Lymph node metastasis				
Non - melanoma	5	5	-	1 2)
Melanoma	2	-	2	-
Parotid gland	3	2	1	-
Soft tissue	9	8	1	1 2)
Melanoma				
Skin	4	1	3	-
Choroid	6	3	-	-

1) : In one patient of 3, the treatment was prescribed to manage the tumor recurred after radical radiotherapy.

2) : The complications developed in the patients with recurrent tumor following radical radiotherapy.

Table 6 Results of Treatment with Protons (70 MeV) for Choroidal Melanoma : NIRS (October,1986)

Patient Code	Age	Sex	Sites	Field Size (mm)	Dose Gy / Fr./ Days	Effect Tumor	Effect Eye	Length of Follow-up
56938	44	F	Choroid *	10 o	30 / 3 / 22	3	1	10 Mo.
57164	45	M	"	13	50 / 3 / 29	3	1	7 "
57174	44	M	" *	10	50 / 5 / 36	2	2 [1)]	7 "
57278	58	F	"	25 x 17	60 / 5 / 43	4	2 [2)]	5 "
57325	22	F	"	13	50 / 5 / 29	2	1	4 "
57408	34	M	" *	13	50 / 5 / 29	2	1	4 "

* : Tumors, located ajacent to optic nerve.

1) : Edema of the retina. 2) : Skin reaction (Erythema).

melanoma, and on the progress of physical studies for fast neutrons. Thereafter, the institutions in the other European countries and the hospitals in U.S.A. and Japan participated to the clinical trials.

The results show that, although the late radiation effects developed in soft tissues and pelvis were severer than those of photon beam irradiation, the patients who received fast neutron therapy have had improvement of local control of the tumor compared with the series of photon irradiation when the indication for fast neutrons was appropliately decided.

Another results show that the side effects developed after fast neutron therapy were strongly dependent on the physical factors of the beams, because almost all accelerators used for clinical trials were the machines originally equipped for physical studies and produced the beams with inadequate penetration in the tissues, and that, when the high energy neutrons were used, the rates of complications in the pelvis markedly reduced.

Therefore, it was suggested that the treatment with high LET radiations have to be carried out under conditions, where the penetration of thebeam should be equivalent to high nergy x-rays and side scattering of the beam should be low as much as possible.

Based on the evaluation of the treatment with fast neutrons and protons, project studies for medical use of accelerated heavy ions, characterized by high LET as well as Bragg peak, were organized at NIRS, and design studies to make Heavy Particle Medical Accelerator were conducted. The synchrotron, which is the main accelerator of the project, will accelerate the Silicon ions up to 600 MeV / amu, which allow to make Bragg peak at 20 cm depth of the tissues (Fig. 9).

At NIRS, the treatment with fast neutrons and protons have been conducted to improve the results of radiation therapy with megavoltage radiations.

The accelerated heavy ions will provide a new era for radiaiton therapy where the radiations are able to use as the surgical knife in cancer treatment.

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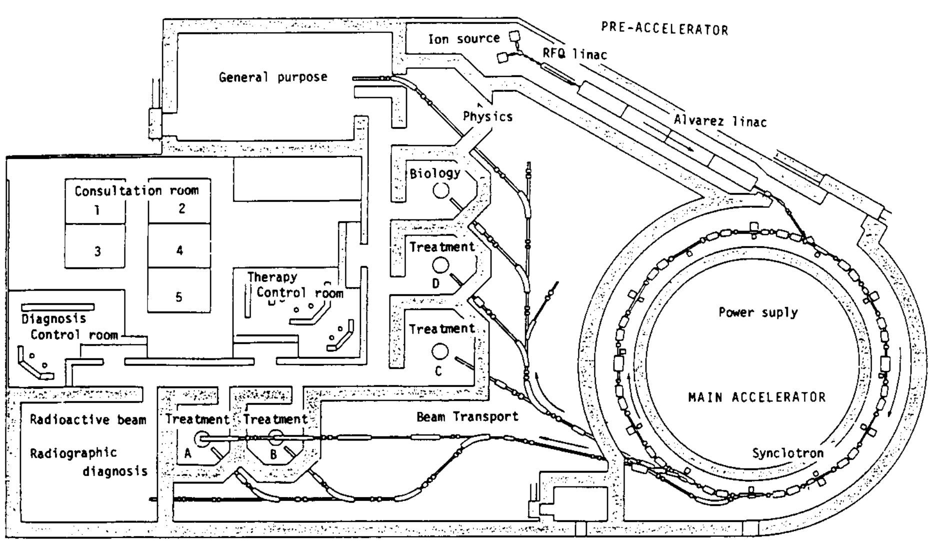

Fig. 9 Preliminary Illastration of the NIRS Heavy Particle Medical Accelerator and the Beam Lines for Cancer Treatment (NIRS)

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