PROTON THERAPY AT PNPI SYNCHROCYCLOTRON

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Introduction

The world's experience in clinical radiation therapy with heavy charged particles, mainly with protons and alpha-particles, includes over 14000 patients. At present, medical proton centres are functioning in the USA, Canada, Japan, Russia, and in other countries. Considerable clinical experience has been accumulated in application of the proton beams for treatment of the hormon-dependent forms of cancers, such as cancer of mammary glands, prostate, and uterine cervix, as well as adenomas of hypophysis, diabetic angioretinopathy, malignant tumours of eyes, arterio-venous malformations, etc.

The advantage of the high energy proton beam is low scattering of the protons in the tissue. This allows to form the dose fields with high edge gradients that is especially important in the cases when the irradiation is used for selective damage of the volumes which are in immediate proximity to the life-critical organs. Usually the protons used for irradiation have the energy of 70–200 MeV, their range in the biological tissues being appropriate to the location of the irradiated neoplasm. The effect of enhancement of the proton ionization losses at the end of the range (Bragg peak) helps to shape the proper dose fields. To strengthen this effect, a technique of multiple irradiation of the selected zone from various directions is used, the integral dose in this case being distributed over a large area at the body surface.

The Gatchina synchrocyclotron has a fixed energy of the extracted proton beam – 1000 MeV. The high energy protons easily penetrate through the irradiated object producing a uniform ionization along their track. Due to low scattering of the protons in the tissue, a narrow beam with sharp edges formed at the entrance of the irradiated object retains practically the same shape in the irradiated zone inside the object. With such irradiation method combined with the rotation technique it is possible to provide a very high ratio of the dose in the irradiated zone to the dose at the object's surface.

The studies of this irradiation method began at PNPI in 1971 jointly with the Central Research Institute of Roentgenology and Radiology using one of the physical beams of the synchrocyclotron. In 1973 the studies were continued in a specially built medical facility which included a medical proton tract and a therapy building with a hall for irradiation. Detailed experimental studies of the dose distribution in tissue equivalent phantoms, radiobiological studies of small biological objects (yeast, tumour cells of animals) and on dogs justified the clinical application of the 1 GeV proton beam approbated then by the Committee on New Medical Technique of the USSR Ministry of Health.

Since 1975 the PNPI medical proton beam was systematically used for proton therapy. By June 1996, the course of proton therapy has been given to 985 patients. The accumulated experience in clinical application of the 1000 MeV protons shows that the most optimal area is the radioneurosurgery. It should be pointed out that this method can be used even in inoperable cases and with the weakened patients.

Proton therapy centre

The PNPI proton therapy centre exploits a special beam line leading to a hall where the installation for proton stereotaxic therapy is located. The beam parameters and the irradiation process are controlled from a special control room. The medical centre includes also a small clinics (20 beds) where the patients could spend a short time preparing for the therapy seance. The scheme of the proton tract and the installation for irradiation are shown in Fig. 1. The extracted from the synchrocyclotron proton beam is collimated by the beam shaping collimator which regulates the size of the beam spot. Then the beam is deflected by the bending magnet and focused onto the irradiation plane with a doublet of quadrupole lenses. The total length of the beam line is 70 m. Besides the beam shaping collimator, there is no other collimators in the beam line except a wide opened anti-halo collimator in front of the quadrupoles. Such a simple scheme allows to obtain in the irradiation zone a narrow beam 6 mm in diameter with sharp edges. All the way from the entrance into the beam shaping collimator to the exit from the quadrupoles the beam is transported in a vacuum pipe to prevent the multiple scattering and inelastic interactions of the protons in the air. The irradiation hall is separated from the synchrocyclotron by two shielding walls made of iron and concrete blocks. Finally, the beam is damped by the iron trap in the irradiation hall. The radiation background in the hall is quite low, and it is determined mostly by the interaction of the beam with the irradiated object. The beam position, profile, and intensity are under permanent control. Any deviation of the beam parameters beyond the preset limits stops immediately the acceleration process in the synchrocyclotron thus excluding completely any danger of over-irradiation of the patient.

Fig. 1 shows also the movable table which provides pendulum-like oscillations in the horizontal plane around the Z-axis within $\pm 40°$. The anteriour part of the table represents a head fixation device which can perform independent pendulum-like oscillations around the X-axis within $\pm 36°$. The crossover of the X and Z axes is the centre of rotation (isocentre). The adjustment system allows to position the isocentre precisely in the beam axis. Then the patient's position on the table is regulated in such a way that the zone selected for irradiation would be exactly in the isocentre. This zone is determined beforehand in the hospital, and its coordinates are fixed relative to the reference points in the head bones. The installation procedure is performed with the help of a special head mask under control of a high sensitivity X-ray setup which has two fixed positions - along the Z-axis and along the beam axis. The final precision of the installation is better than 1 mm. The rotations of the patient's table and the head fixation device are programmable. Fig. 2a shows two modes of operation – the consequent and simultaneous rotations. The spatial distribution of the radiation dose achieved by this method is demonstrated in Fig. 2b. An important feature of this distribution is the fast decrease of the dose along the X- and Z-axes. The ratio of the radiation dose at the head surface to that in the isocentre is 1/200. The dose absorbed by the thorax organs does not exceed $3 \cdot 10^{-5}$ of the dose in the isocentre.

The measurements of the dose distribution were performed with the phantom imitating the human head and the body using miniature thermoluminescent detectors calibrated with the ionization and activation methods. The precision in the relative measurements was $\pm 3\%$ and that in the absolute measurements was $\pm 4\%$. Also, these studies allowed to calibrate the beam monitor which was used to control the radiation dose received by the patients.

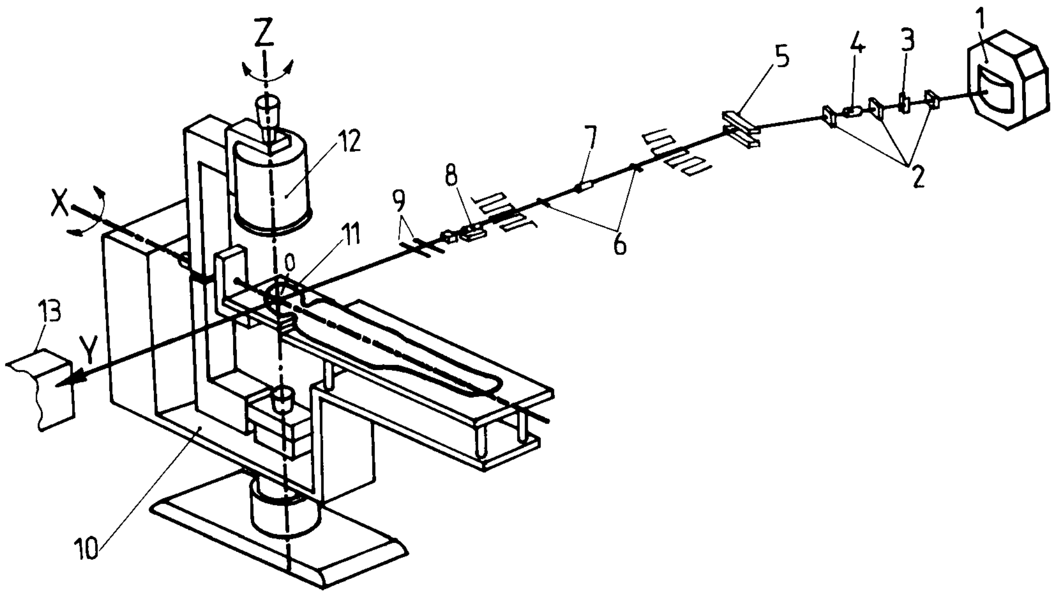

Fig. 1. Medical proton tract and the irradiation facility.
1 – synchrocyclotron; 2 and 6 – profilometers; 3 – magnetic corrector; 4 – beam shaping collimator; 5 – bending magnet; 7 — anti-halo collimator; 8 – doublet of quadrupoles; 9 – multiwire proportional chambers; 10 – patient's table; 11 – head fixation device; 12 – X-ray setup; 13 – proton beam absorber.

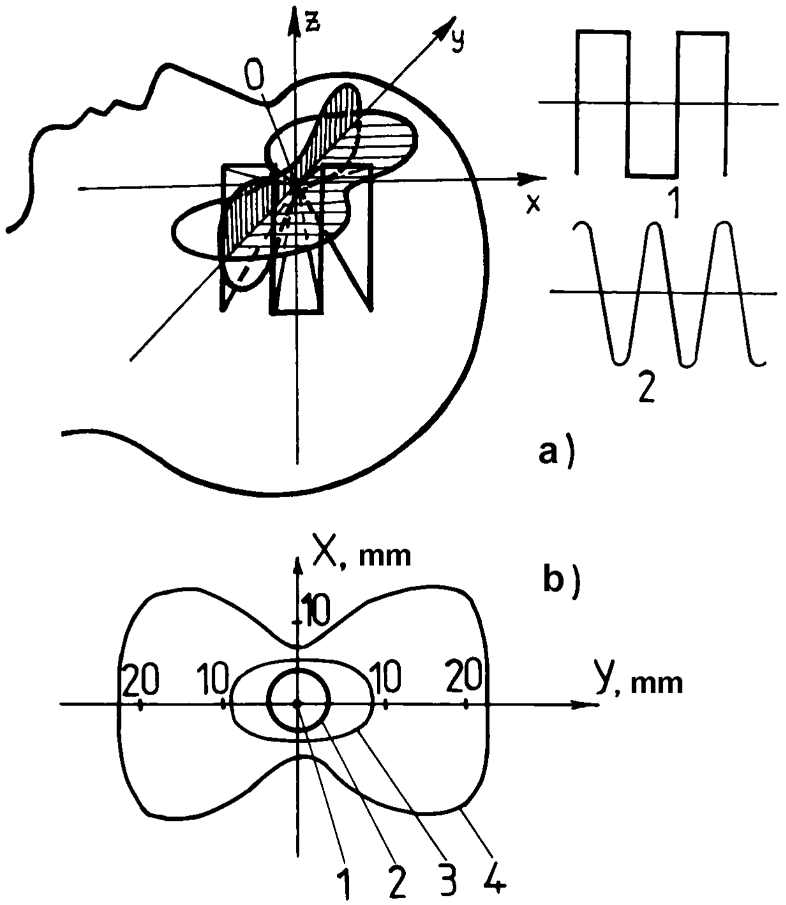

Fig. 2. a) Scheme of the patient's head rotation around X- and Z-axes. The proton beam is directed along the Y-axis. 1 – the beam trajectory at the patient's head surface at consecutive rotations of the patient's table and the head fixation device; 2 – the same at simultaneous rotations.
b) Spatial distribution of the radiation doses. Isodoses: 1 – 90%, 2 – 50%, 3 – 20%, 4 – 5%. The beam size: $\Delta X = 6$ mm, $\Delta Z = 6$ mm at 50% isodose.

The relative biology efficiency of irradiation with the 1000 MeV proton beam was thoroughly investigated in comparison with the standard X- and γ- radiation methods. It was found that the biology efficiency of these methods is quite similar (Table 1).

Table 2 summarize the main parameters of the proton beam at the PNPI Proton Therapy Centre.

Table 1

Relative biological efficiency (RBE) of the 1000 MeV protons

N	Biological object	Test	Types of radiation. Absorbed doses, Gy	RBE
1	Laboratory line of drosophila wild type p-80	Rate of dominant mutations	1000 MeV protons; 180 keV X-rays 10 – 50	0.76
2	Zeidel's ascitic hepatoma	Tumor inoculation. Lifetime of animals-tumour-bearers	1000 MeV protons; 200 keV X-rays 10 – 20 30 – 40 50	1.0 0.87±0.03 0.60±0.03
3	Erlich's ascitic carcinoma	Inhibition degree of tumor growth; increase of radiosensitivity by means of chemical radiosensibilizators Xantobin	1000 MeV protons; 200 keV X-rays 10 – 20	1.0
4	Hela G-63 cells	Survival	1000 MeV protons; ^{137}Cs γ-radiation 1 – 8	1.0
5	Culture of the haploid prototrophic strain of yeast cells	Survival	1000 MeV protons; 180 keV X-rays 0.1 – 10	0.61

Table 2

Main technical parameters of the medical proton beam

Proton energy	1000 MeV
Energy spread	±10 MeV
Extracted beam intensity	10^9 s^{-1}
Beam size (at 50% isodose)	5–10 mm
Beam divergence	0.5^o
Macropulse repetition rate	up to 50 Hz
Macropulse duration	300 μs
Rate of the absorbed dose	up to 50 Gy$\cdot$ min^{-1}
Edge gradient of the dose field	20% mm^{-1}
Ratio of the dose in the isocentre to that at the head surface	200 : 1
Relative biological efficiency	1.0

Status of practical application of the PNPI medical proton beam

The regular treatment of patients at PNPI began in 1975. The diagnosis of the decease and the recommendation for the proton therapy treatment was done by the specialists in the St.Petersburg's hospitals (mostly Neurosurgery Institute). All the preparation work with the patients was performed at the Central Research Institute of Roentgenology and Radiology. This work included the localization of the zone for irradiation relative to the reference points on the head surface and preparation of the special head mask used to fix firmly the patient's head on the table for irradiation. In this way a group of 20-30 patients was prepared, and they were transported to the PNPI clinics a day before the medical run was scheduled at the synchrocyclotron. The time necessary for positioning of the patient on the table for irradiation is 15-20 min, and the irradiation time ranges from 8 to 20 min. The oscillation movement of the patient's head proceed quite slowly, so the patients practically do not notice it. The proton therapy is painless, and it is carried out without anaesthesia. During the irradiation process the doctors perform continuous control of the patient's state (pulse, breath rate, ECG). There is also a television control and audio communication with the patient from the control room. After the irradiation the patients are transported back to the hospitals at St.Petersburg for further survey.

The dynamics of the patient's treatment is given in Table 3. In all the cases the technical conditions of the irradiation were practically identical: the beam size was 5–7 mm at the 50% isodose, the oscillation angles of the head fixation device and the table deck were $\pm36°$ and $\pm40°$, respectively; the absorbed doses were 120–150 Gy for normal hypophysis, 100–120 Gy for pituitary adenomas, 40–70 Gy for arteriovenous malformations, and 100–120 Gy for epilepsy. In the cases of large pituitary adenomas two- or three-zone irradiation was used.

Table 3

Status of proton stereotaxic therapy at PNPI synchrocyclotron

Disease	1975– –1979	1980– –1984	1985– –1989	1990– –1994	1995– –1996**	Total number of patients
Mammary gland cancer	44	29	20	15	3	111
Prostatic cancer	–	–	1	4	3	8
Ophthalmopathy	4	19(1)*	4	12	10	49(1)*
Diabetic retinopathy	1	13	11	–	–	25
Pituitary adenoma:						
a)Icenko-Cushing's syndrome	5	18	31(1)*	31	5	90(1)*
b)prolacactinic	8	25	42	19	2	96
c)somatotropic	27	66	65(3)*	22	8	188(3)*
d)hormon-non-active	5	11	9	6	–	31
Cerebral malformations:						
Arteriovenous	12	83(10)*	92(19)*	150(72)*	39(21)*	376(122)*
Arterial	1	5	–	–	–	6
Epilepsy	2	3	–	–	–	5
Total number	109	272(11)*	275(23)*	259(72)*	70(21)*	985(127)*

* Repeated proton therapy
** Data for June 1, 1996

Proton therapy of pituitary adenomas (PA)

In treatment of the somatotropinomas (188 patients) clinical remission during the period from 1 to 10 years was achieved in 83% of the macroadenomas cases. The remission was manifested by regress of the acromegaloid syndrome, by normalization of the carbohydrate exchange, and by restoration of the working capability. The concentration of the growth hormones in blood was reduced, and in 5 years it was within the limits of physiological fluctuations (2.8 ± 0.3 μg/l). Stabilization of the symptoms was observed in 4%, while there was no effect in 13% of the cases (mainly, in the cases with pituitary adenomas) when the initial symptoms of the tumor spread out of the borders of the turkish saddle.

In treatment of the prolactinomas (95 patients) the clinical remission was stated in 80% of the cases (the patients with microprolactinomas). It was accompanied by disappearance of the galactorhea, by restoration of the ovarian menstrual cycle, and by decrease or normalization of the prolactine concentration. Thirty women had a pregnancy which ended in a live birth. The stabilization was observed in 17% and no effect was found in 3% of the cases.

In treatment of the corticotropinomas (90 patients) clinical remission was observed in 90% of the cases. In these cases the progression of the Icenko-Cushing's syndrome was stopped already in 3 months after the irradiation, its regression was observed in 6 months. There was decrease of ACTG and of the cortisone secretion, as well as restoration of the daily secretion rhythm. Stabilization was observed in 4% and there was no effect in 6% of the cases. In the treatment of the hormon-non-active pituitary adenomas (31 patients) the clinical remission was observed in 97% of the cases.

Proton therapy of cerebral arteriovenous malformations (AVM)

376 patients with the AVM were divided into two groups according to the AVM volume: the first group — AVM volume less than 8 cm^3, the second group — AVM volume larger than 8 cm^3. The absorbed doses ranged from 40 to 80 Gy.

The angiographic control performed after the irradiation showed that the positive effect had been achieved in 74% of the patients with the AVM volume less than 8 cm^3. The complete elimination of the AVM from the blood circulation was obtained in 65% of the cases. This process continued for a year after the proton therapy.

Only 27% of the patients from the second irradiation group showed a positive effect.

After the proton therapy the majority of the patients revealed a complete or partial regress of the neurologic symptoms, discontinuation or decrease of the rate and degree of the epileptic attacks.

None of the patients revealed any complications in the nearest or in the distant (up to 10 years) terms.

The accumulated experience allowed to establish the indications for possible application of this method: the proton therapy is recommended to the patients with a deeply located cerebral AVM with the volume less than 8 cm^3, including the patients with inoperable AVM.

Proton therapy of endocrine ophthalmopathy (EO)

The method of precision single-run irradiation of the adenohypophysis with the proton beam (the doses of 100–120 Gy) allowed to obtain the positive effect – regress of ophthalmopathy for 29 patients. Prior to the proton therapy, the applied medicinal therapy in these cases was non-effective or the positive effect was transitory. Those patients had a severe progressive EO of the stage II or III, with the pronounced infiltration at the background of the diffuse toxic goitre, as a rule without symptoms of thyreotoxicosis.

In severe forms of the infiltrative EO, before the proton therapy an intensive medical treatment had been given before PST by corticosteroids in maximum doses up to 80 mg/day, thereafter the hypophysis was irradiated. There was observed not only subjective (elimination of the photophobia, of the colic and pain in the eyes, of the fatiguability of the eyes at visual loads), but also an objective improvement of the state according to the data of ophthalmometric and ophthalmoscopic examinations.

Proton therapy of diabetic angioretinopathy (DR)

As to the diabetic angioretinopathy, our experience includes the treatment of 25 patients (9 men and 16 women). The focal dose for the adenohypophysis was 100–120 Gy. For patients with the visual function within 0.5–0.7 in the stage of hemorrhagia or in the initial phase of the exudative changes in the eye fundus, the stabilization and regression of the angioretinopathy symptoms was observed (plasmorrhagia and amount of microaneurysms were decreased; hemorrhages in the fundus of the eye had stopped; visual function had been stabilized, and improved in some cases).

The proton therapy prognosis in DR cases depends on many factors, firstly, on the state of diabetes mellitus compensation, its severity and duration.

Conclusion

The utilization of the 1000 MeV proton beam for proton therapy at the PNPI Medical Centre demonstrated the efficiency of this method. The main advantage of the high energy protons is low scattering in the human body. In combination with the rotation irradiation technique, this allows to deliver large radiation doses to the small zones selected for irradiation without damaging the neighbour areas. This advantage is especially valuable in the radioneurosurgery. The many-years experience accumulated at PNPI with nearly 1000 patients showed also a high reliability and safety of the method. None of the patients treated at the PNPI Proton Therapy Centre had any complications related with the quality of the radiation process. Nowadays, this method is widely recognized among the medical specialists and has good perspective for extensive application. The description of the PNPI medical facility and the results on the proton therapy are presented in Refs. [1–6].

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