STEREOTAXIC 1000 MeV PROTON THERAPY AT THE PNPI SYNCHROCYCLOTRON

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1. Introduction

At present the hadron (proton and light ions like ^{12}C) therapy is used successfully for the treatment different types of oncological tumors. Since the beginning of radiological bloodless surgery in 1961 till today more than 50000 patients were treated at 40 medical centers over the world. Figure 1 illustrates the progress in putting into operation medical centers with a number of treated patients more than 1000. On histogram the start year of center's operation is given. The PNPI-RSCRST medical complex as one of the first proton facilities has a long-term experience in the radiotherapy of brain diseases. All acting irradiation centers use in the irradiation treatment so called method of "Bragg peak" required proton energy of 200–250 MeV. PNPI uses in stereotaxic therapy protons with E_p = 1000 MeV, that is the unique method over the world. The advantage of the high energy proton beam is a low scattering of protons in the tissue.

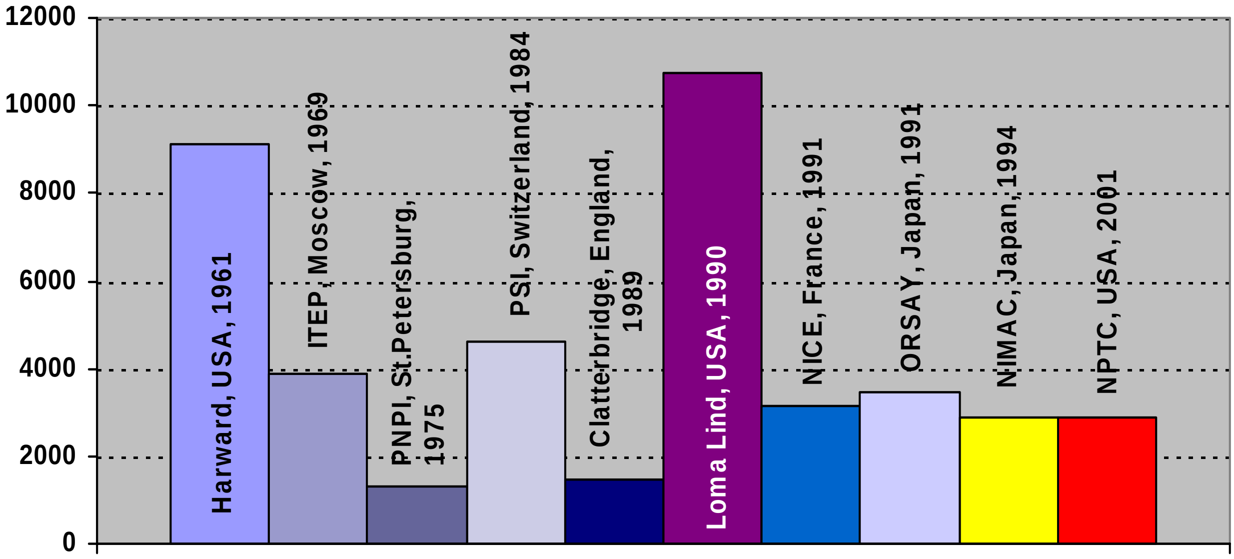

Fig. 1. Medical centers over the world with a number of patients more than 1000 treated by hadron therapy

Protons of this energy easily penetrate through an irradiated object producing a uniform ionization along their tracks. Due to low scattering of protons in the tissue, a narrow beam with sharp edges can be shaped at the entrance of the irradiated zone inside the object. Such irradiation method combined with two ways rotation technique allows to provide a very high ratio of the dose in the irradiated zone to the dose at the object's surface. Dose fields with high edge gradient obtained by such method are especially important in the cases when the irradiation is used for selective damage of the volumes placed in immediate proximity to the life-critical organs. Our method gives the most effective results at proton treatment of pituitary adenomas and arterio-venous malformations as well as the hormone-dependent forms of mammary gland and prostate cancer, *etc*. Detailed publication of PNPI method of proton therapy and obtained results during 1975–1996 are given in Refs. [1, 2]. In this paper we present the results of 1000 MeV proton steriotaxic therapy different head brain diseases performed during 2002–2006 and the description of a medical beam upgrade which has been done in 2003–2004.

2. Technical features of proton therapy facility

The PNPI proton therapy facility is based on the synchrocyclotron with fixed energy of proton beam (E_p = 1000 MeV), which was built for the purpose of research on the nuclear and particle physics at intermediate energies. Artistic view of synchrocyclotron is shown in Fig. 2. The current inside the vacuum chamber of the accelerator is 3 μA. The intensity of the extracted beam in the accelerator hall is 1 μA. The accelerator has three beam lines for the transportation of proton beams into the experimental hall with fixed energy of 1000 MeV with regulated intensities in the range 10^7–10^{11} proton/sec.

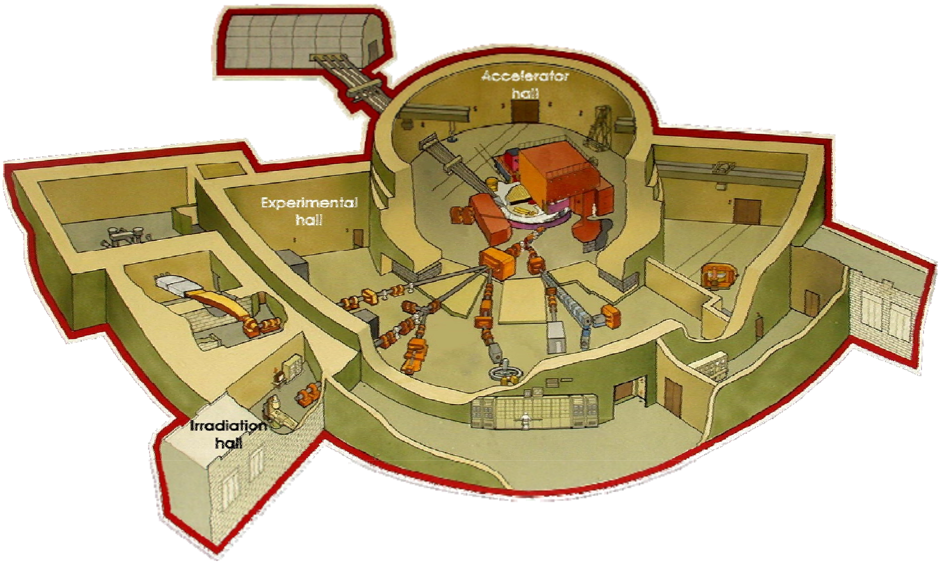

Fig. 2. Artistic view of synchrocyclotron and experimental halls

Extracted from the accelerator medical proton beam (Fig. 2) is produced by beam shaping collimator placed just at the entrance of the beam channel. It regulates the size of beam spot and consequently the intensity of the beam. Then the beam is deflected by bending magnet and focused by quadrupole lenses onto the irradiation hall (Fig. 3). The total length of the beam line is 70 m. The antihalo collimator is installed in the experimental hall. Such simple beam optics scheme allows to obtain in the irradiation zone a narrow beam of 6 mm in diameter with sharp edges. The beam is transported in a vacuum pipe to prevent the multiple scattering and inelastic interactions of protons in the air. The irradiation hall is separated from the experimental hall by two shielding walls made from iron and concrete provided the radiation background in the hall at quite low level. The beam position in the accelerator and experimental halls as well as in the irradiation hall and the beam intensity are under a permanent control from the accelerator and medical control

Fig. 3. Irradiation hall

rooms. Any deviation of the beam parameters beyond the reset limits stops immediately the acceleration process in the synchrocyclotron thus excluding completely any danger for irradiated patients. In 2002–2004 the upgrade of proton medical beam-line has been done including the construction of new collimators and special profile-meters of proton beam in accelerator and experimental halls.

In this paper we present the upgrade of proton beam-line only in the irradiation hall. Profiles in the irradiation hall are measured by two multiwire proportional chambers (X0Z plane) with a gold-tungsten anode wire of 20 μm diameter and stainless steel cathode wires of 50 μm diameter. The wire spacing is 1 mm, the surface of entrance window is 128 × 128 mm^2.

The final proton distribution at the position of patient head on the rotation table is measured by the silicon detector precisely moving along the X-axis by step of 153 μm and along the Z-axis by 9 μm. The range of such scanning is 25×25 mm^2. Profiles of proton intensity at the isodose center of irradiated target is shown in Fig. 4. The intensity of proton beam in the irradiation hall is measured by MWPC in current regime and then transformed into dose distributions, which are periodically calibrated by diamond detectors.

The constancy of a planning dose for each patient irradiation is controlled from accelerator and medical control rooms. The dose distribution during the patient irradiation is shown in Fig. 5. All elements of proton medical beam-line were upgraded by the installation of new mechanical systems and the change of electronics of all detectors to the contemporary base ones. The movable patient's table seen in Fig. 3 provides pendulum-like oscillations in the horizontal plane around the Z-axis within ±40°.

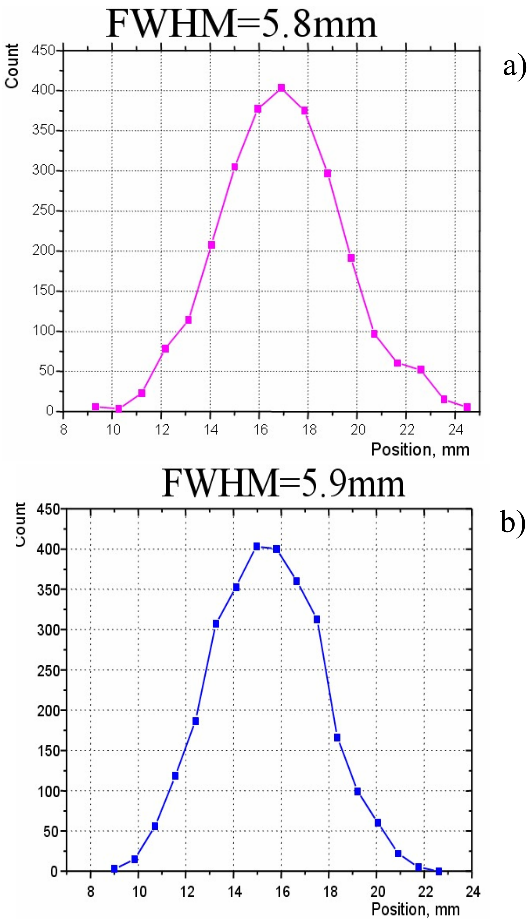

Fig. 4. Vertical (a) and horizontal (b) profiles of proton beam at the isodose center of irradiated target

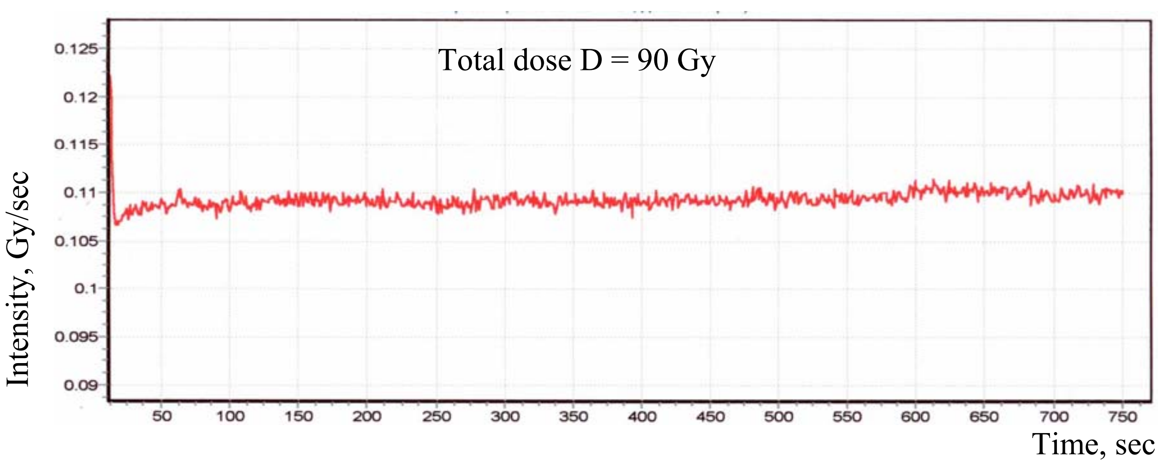

Fig. 5. Distribution of proton beam intensity during the patient irradiation

The anteriour part of the table represents a head fixation device performing an independent pendulum-like oscillation about the X-axis within ±36°. The crossover of the X- and Z-axes is the center of rotation (isocenter). The adjustment system allows to locate the isocenter 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 center. This zone is determined in the hospital by computer tomography, and its coordinates are put in the protocol. The installation procedure in the irradiation hall is performed by means of a special head mask under the control of a high sensitive *X*-rays setup, which has fixed positions – along the Z-axis and along the beam Y-axis. The final precision in such installation is better than 1 mm. Figure 6a shows the scheme of simultaneous rotation of the patients table and head fixation device and also beam trajectories on the patient's head. Figures 6b-c show the dose distributions in X0Z and X0Y planes, which characterized very sharp decreasing in both directions.

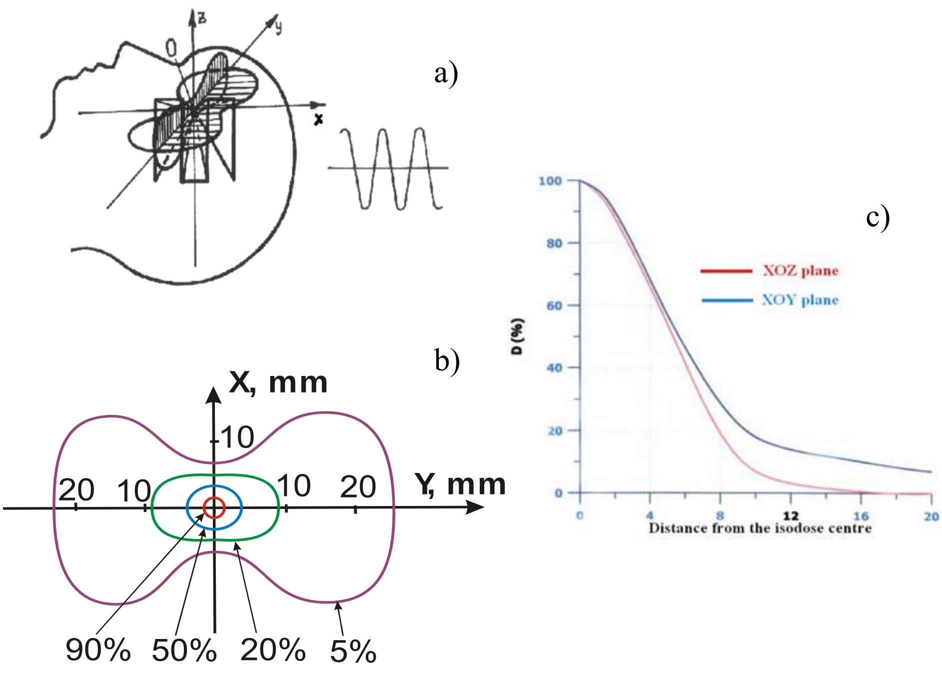

Fig. 6. Scheme of the patient's head rotation around Z- and X-axes. The proton beam is directed along Y-axis. a) The beam trajectories over the patient's head surface at simultaneous rotation of patient's table and head fixation device. b) Spatial distribution of the radiation dose for beam size X = Z = 6 mm. Isodoses: 1 – 90%, 2 – 50%, 3 – 20%, 4 – 5%. c) Profiles of dose distribution in planes X0Z and X0Y (distance in mm)

3. Patient's treatment procedure and results of the therapy

The procedure of patient's treatment is the some as it was described in Ref. [1]. This work included the localization of the zone for irradiation relative to the reference points on the head surface and the preparation of the special head mask used to fix firmly the patient's head on the table for irradiation. The time necessary for positioning of the patient on the table for the irradiation is 15–20 min, and the irradiation time ranges from 8 to 20 min. The oscillation movements 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 anesthesia. 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. Statistics of proton therapy at the PNPI synchrocyclotron is presented in Fig. 7.

The dynamics of patient's treatment in 2002–2006 is shown in Fig. 8. Unfortunately, it has a negative tendency and the number of patients treated for this period is less than the corresponding number during 1985–1989 by a factor of two. In some cases such tendency can be explained by the increased competition between neurosurgical and radiological methods of patient's treatment. We observed in the case of pituitary adenomas increased number of patients undergoing a prior surgical operation but not always successful.

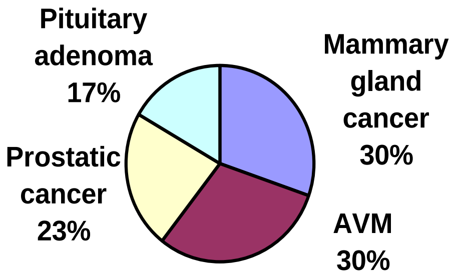

Fig. 7. Number of patients treated at the PNPI–RSCRST medical center during 2002–2006. Pituitary adenoma – 17%, AVM – 30%, mammary gland cancer – 30%, prostatic cancer – 23%. In total 132 patients

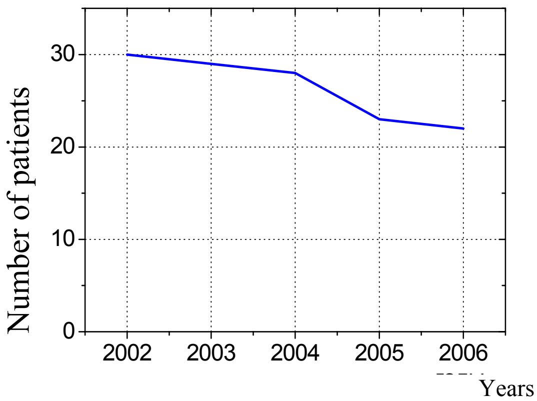

Fig. 8. Dynamics of treated patients

Other possible reason of partient's number reduction can be the total decreasing of inhabitants in Russia, especially in the North-West region of former USSR.

3.1. Proton therapy of pituitary adenomas

Pituitary adenomas comprise about 10–12% of all intracranial tumors [1]. They can be classified as benign histologically but can cause morbidity and occur through hormonal inbalances and functional deficits. Various radiation techniques such as gamma knife and linear accelerator-based stereotaxic radiosurgery [2] as well as charged-particle therapy [3,4] are used for the treatment of such diseases. The application of narrow 1000 MeV proton beam for the irradiation of intracranial tumors (Gatchina transmission method [1]) is very effective, especially in the treatment of different pituitary adenomas. In the case of the somatotropinomas in total 201 patients were treated during 1975–2006. The clinical remission observed during from 1 to 10 years was achieved for 83% patients with macroadenomas. The remission was manifested by the disappearance of tumor growth, the regress of the acromegaloid syndrome, the normalization of carbohydrate exchange and the restoration of working capability. In Fig. 9 the distribution of growth hormone (GH) concentration in blood of patients before and after proton therapy at the dose of D = 80 CGE observed during 5 years is shown. The number of patients analyzed during five years is 85.

It is seen in Fig. 9 that after 5 years the GH concentration is within the limits of physiological normal value 2.8 ± 0.3 ng/ml. The stabilization of symptoms is observed for 4% of patients, while there is no effect in 13% cases mainly when initial symptoms of the tumor arte spread out of borders of the turkish saddle. In the treatment of the prolactinomas (115 patients, 4 of them in 2002–2006) the clinical remission was stated in 80% cases of patients with microprolactinomas. It was accompanied by the disappearance of the galactorhea, the restoration of the ovarian menstrual cycle, the decrease of prolactin concentration and the stop of tumor's growth. In Fig. 10 the change of prolactin concentration in blood of treated patients after proton irradiation is shown. After 5 years such level is close to the normal one, corresponding in average more than 50% its reduction. Thirty women had a pregnancy ended in a live birth. The stabilization was observed in 17% cases, in which the decrease of prolactin concentration was less than 50%. The treatment of corticotropinoma adenomas (Icenko-Cushing's syndrome) is the most successful kind of pituitary adenoma proton therapy. From 205 (10 in 2002–2006) treated patients the clinical remission was observed in 96% cases, the stabilization – in 1%, and only in 3% cases there was the progress in the growth of a tumor.

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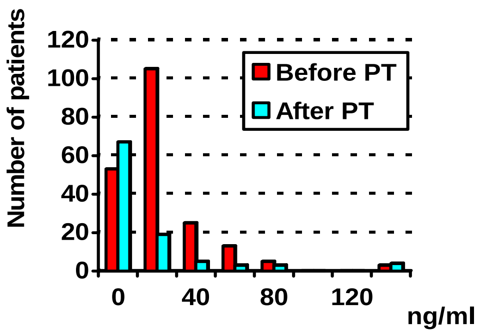

Fig. 9. Distribution of GH (growth hormone) concentration of patients before and after proton therapy (PT) for 5 years observation. Somatotropic pituitary adenoma.
Total number of patients before PT is 201

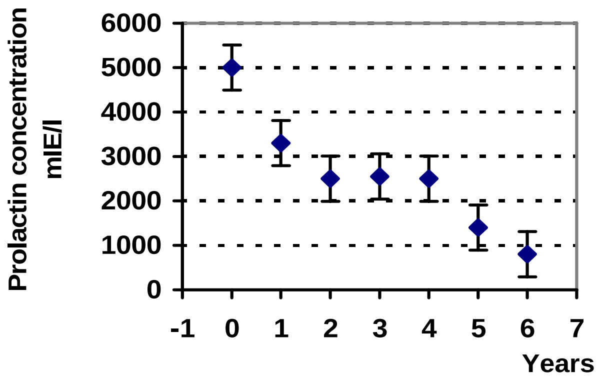

Fig. 10. Dependence of prolactin concentration as a function of time observation patients after proton therapy

In the case of the clinical remission the Icenko-Cushing syndrome was stopped already after 3 months of the irradiation. One can observe the decrease of ACTG and the cortisol secretion as well as the restoration of daily secretion rhythm. Women undergoing proton irradiation further had normal pregnancy and gave birth to child without the indication of endocrin pathology. Photo of patient K. (woman since 19 years suffered from Icenko-Cushing's syndrome) before (2003) and after (2005) proton irradiation at D = 80 CGE with normal child is shown in Fig. 11. One can note that usual neurosurgical operations do not give women the possibility to have pregnancy and to give birth to a child.

Fig. 11. Photos of patient K. with Icenko-Cushing syndrome before and after proton therapy

3.2. Proton therapy of cerebral arteriovenous malformations (AVM)

Surgical practice shows that only about 50% of AVM is medicable in clinics, especially in cases when AVM is placed in critical or inaccessible zones of head brain. Proton therapy of AVM with rather small volume – not more than 8 cm^3 – gives the positive result in 74% cases without any influence on neighboring life-important parts of the brain at doses of 40–80 CGE. The complete elimination of the AVM from the blood circulation is observed in 65% cases. This process continued for a year after the irradiation. For AVM's volume appreciably more than 8 cm^3 only in 27% cases one can have the positive result. After the proton therapy the majority of patients revealed a complete or partial regress of the neurologic symptoms, discontinuation or decrease of the rate and degree of epileptic attacks. The total number of patients treated in 1975–2006 is 491, in 2002–2006 – 40, from them 144 patients were treated secondly. To improve results of AVM's large volume treatment it is necessary to develop new methods of proton steriotaxic therapy or to use beams of more dimensions.

3.3. Proton therapy of mammary glands and prostatic cancer

In 2002–2006 the treatment of 40 patients with mammary gland cancer and 30 patients with prostatic cancer have been performed. The total number for 30 years is 184 and 117, correspondingly. In such treatment the irradiation of special zones of pituitary gland was used.

4. Proposal for 200 MeV proton therapy at PNPI-RSCRST medical center

As it was written above, the number of patients treated in last years at 1000 MeV proton beam is decreasing due to some reasons, main of which is the small number of patients with intracranial diseases of head brain in St.-Petersburg and even over the North-West region of Russia. According to estimates of different experts, the number of patients with pituitary adenomas, AVM and some others are approximately 2–3% of total patient's number with oncological tumors. For example, in St.-Petersburg there are about 100000 citizens suffered by cancer and every year this quantity is increasing by 20000 new patients. The PNPI method of stereotaxic 1000 MeV proton therapy is unique over the world; this method shows better results in pituitary adenoma treatment than widely used Bragg peak method and it needs to continue its performance with some upgrade of diagnostic tools. Taking into account very sharp necessity of St.-Petersburg in radiotherapy, which is satisfied only on 6–7%, the PNPI-RSCRST Medical Center suggests to use for the treatment of wide spectrum of cancer's diseases a new proton beam of 200–250 MeV providing the irradiation of patient's tumor by the Bragg peak method. Such proton beam is obtained by lowering the initial proton energy (1000 MeV) in a degrader, placed just at the exit of accelerator, up to required energy (see Fig. 2). Then 200 MeV proton beam is transported into the irradiation hall. The PNPI Accelerator Division has already the experience in obtaining 900–200 MeV proton beams for physical experiments [3]. Parameters of a new special medical beam line were calculated using GEANT 3, MESON and OPTIMUM codes. In Figs. 12–13 results of Monte Carlo simulations of horizontal and vertical proton beam profiles as well as the proton momentum distribution at the target position in the irradiation hall are shown. The intensity of the beam is equal to 8×10^8 p/sec, that corresponds to the accumulated dose of 12 Gy/min.

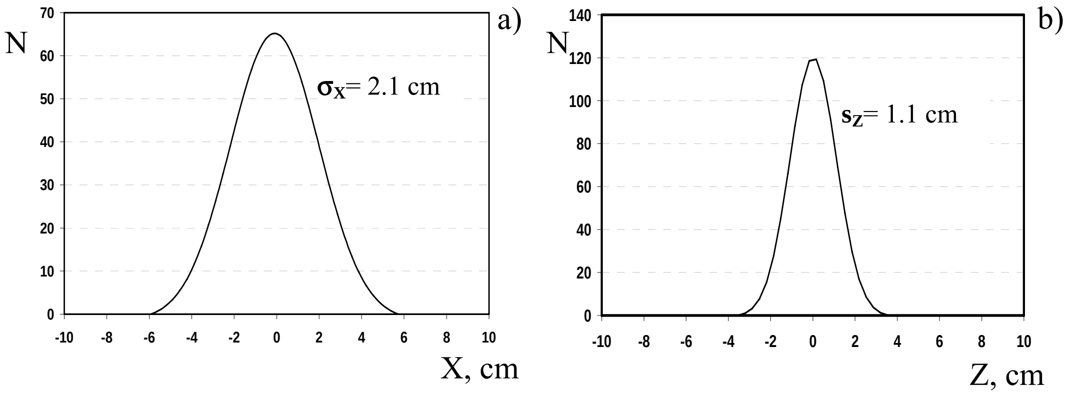

Fig. 12. Horizontal (a) and vertical (b) profiles of 200 MeV proton beam at the place of irradiated target in the irradiation hall. The distance from the exit of 1000 MeV proton beam in accelerator hall to irradiated target is 53 m

Such dose rate is enough for the multifractional irradiation of tumors by area of 15–20 cm^2 and even more using special device for conformal therapy. In the absence of special medical accelerators in Russia the upgrade of existing machines proposed for physics research (as, for example, Dubna synchrocyclotron [5]) to perform hadron radiotherapy is at present a real way in the improvement of total situation in cancer treatment.

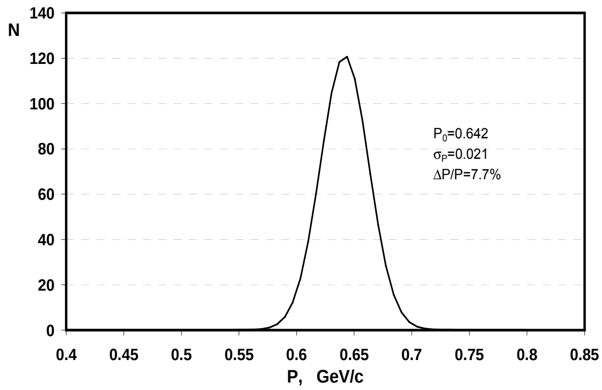

Fig. 13. Momentum distribution of 200 MeV proton beam in the place of the target in irradiation hall

5. Conclusion

The use of the 1000 MeV proton beam for stereotaxic therapy at the PNPI-RSCRST Medical Center has demonstrated the high efficiency of this method. The combination of the rotation irradiation technique and narrow proton beam with sharp edges allowed to deliver large radiation doses to small targets selected for the irradiation without damaging of neighbor volumes in the proximity to the life-critical zones of head brain. The treatment of 132 patients in 2002–2006 and of total 1320 patients for 30 years showed a high reliability and safety of the method, none of the patients had any complications related with the quality of irradiation process. As before 1000 MeV proton therapy can be applied for the treatment of wide spectrum of head brain diseases, in particular, pituitary adenomas. Upgrade of PNPI Medical Facility and the construction of a new 200 MeV beam-line will allow to satisfy in the most extent the need of the North-West region of Russia in bloodless radiosurgery.

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