## 1. Introduction

The malignant tumour death rate is second only to the cardiovascular disease death rate. Every year about three hundred out of a hundred thousand people became ill with cancer, and this figure tends to grow steadily. For example, over the period 1980–1994 in Russia the number of people who were diagnosed with primary malignant tumours increased by 28.5% amounting to 411.8 thousand, and the number of those who died of cancer increased by 34.7% amounting to 300.6 thousand [1].

Now there are basic three methods to treat oncological diseases. they surgery, radiotherapy and chemotherapy. Fundamental research in the field of molecular biology will probably reveal the causes of cancer in the future and thus will be able to indicate the most effective treatment. However, until this happens, the major task is to develop and improve the above methods.

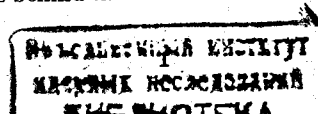
Among these methods radiotherapy is applied to 40–75% of all cancer patients, independently or in combination with the other methods. The current trends indicate that it will become more and more important in the near future [2].

## 2. Brief history of radiotherapy

The main goal of radiotherapy is to produce a lethal effect on all tumour cells with as little damage as possible to normal tissues both around the tumour and inside the tumour volume. Development of radiotherapy has always been intimately related to the search for and application of penetrating radiations whose characteristics are the most suitable for this goal.

Radiotherapy came into being at the turn of the century immediately after Röntgen discovered the X-rays. At the first stage as long as 50 years or so, X-rays of energy up to 300 keV were mainly used in radiotherapy. A high surface dose, low penetration, and too high dose on bone tissues typical of X-rays in the kilovolt energy range often resulted in complications and did not allow successful radiation treatment of deep-lying tumours.

In the past three decades the radiotherapy based on $^{60}$Co gamma-rays, electron beams and bremsstrahlung in the megavolt energy range has been developed. In Fig. 1 one can see depth dose distributions for gamma-rays with energies ranging from 60 keV to 35 MeV [3] and for electron beams with energies ranging from 7 to 28 MeV [4]. Two points are worth noticing. One is a distinct advantage of the megavolt radiation dose distribution. For gamma-quantum beams it is due to higher penetration and a gradual increase in the input dose, which is very important for decreasing the exposure of the skin and subcutaneous tissues. Electron beams feature fast dose variation at a certain depth, which allows a substantial decrease in the dose on normal tissues behind the tumour. The other point is weak variation of



dose characteristics in the gamma-quantum energy range 22–35 MeV and a gentler slope of the dose drop near the end of the electron beam penetration depth at higher electron energy. This behaviour of dose characteristics indicates that there is no point in increasing the energy of electron-photon sources.

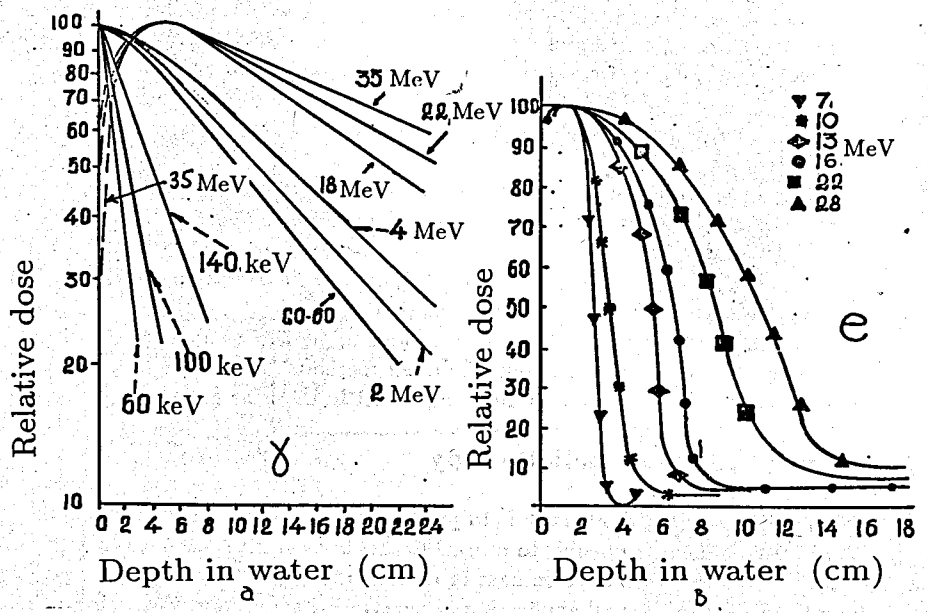



Fig. 1. a) Depth distributions of doses from sources of gamma-rays with energies from 60 keV to 35 MeV [3].
b) Depth distributions of doses from electron beams of energies from 7 to 28 MeV [4].

Substantial improvement depth dose distributions for megavolt radiation sources, more precise dose monitoring, and optimization of radiation treatment planning increased the efficiency of radiotherapy. Table 1 presents the data on increasing survival rate of USA patients with different type malignant tumours treated by megavolt radiation as compared with the kilovolt one [5].

However, despite that impressive progress of radiotherapy in treating some types of malignant tumours, failures are still quite often. In Table 2 there are data on



the number of USA patients who died of cancer after radiation treatment and the estimated number of patients with different tumour locations whose death can be attributed to local and regional radiation treatment failures, more often characterized as recurrent tumours [2].

Table 1. Survival rate of patients with different type malignant tumours treated by megavolt and kilovolt radiation [5].

| Tumour | Survival of patients having 5 years follow-up (%) | |
|---|---|---|
| | Kilovolt radiation | Megavolt radiation |
| Hodgkin's disease (lymphogranulomatosis) | 30 – 35 | 70 – 75 |
| Uterine body cancer | 35 – 45 | 55 – 65 |
| Prostate cancer | 5 – 15 | 55 – 60 |
| Nasopharynx cancer | 20 – 25 | 45 – 50 |
| Bladder cancer | 0 – 5 | 25 – 35 |
| Ovary cancer | 15 – 20 | 50 – 60 |
| Seminoma of testicles | 65 – 70 | 90 – 95 |
| Embryonal cancer of testicles | 20 – 25 | 55 – 70 |

These failures are mainly due to impossibility of delivering a dose to the tumour which would allow it complete sterilization and the same time keep a satisfactory anatomical and functional state of normal tissues inside the irradiated volume. The data of Table 2 indicate that about 30% of patients who died after the radiation treatment could be saved every year provided that improved radiotherapy means and methods were available.

## 3. Grounds for using beams of heavy nuclear particles in radiotherapy

Exposure of normal tissues around the tumour can be decreased by improving only the geometrical factors of dose distribution. This is hardly possible with megavolt electron and gamma-quantum sources. As is evident from Fig. 1, at energies above 20 MeV the longitudinal dose distribution for gamma-ray sources practically does not improve with increasing energy while one of the main electron beam advantages—a sharp dose drop at a certain depth—gradually disappears with increasing energy.

Table 2. Estimated number of patients in the USA who died because of radiation treatment failure [2].

| Tumour location | Yearly death rate as of 1974 the main | Estimated number of patients with local failures as cause of death |
|---|---|---|
| Head and neck | 7900 | 3200 |
| Oesophagus | 6300 | 3700 |
| Mammary gland | 32750 | 4600 |
| Uterine cervix | 7800 | 4700 |
| Uterine body | 3400 | 2000 |
| Ovary | 10700 | 9000 |
| Prostate | 18000 | 11000 |
| Bladder | 9200 | 5000 |
| Brain | 8100 | 7700 |
| Skin | 5100 | 3500 |
| Lungs | 75400 | 8000 |
| Lymphoma | 20400 | 2500 |
| Total | 205050 | 64900 |

Beams of high-energy heavy charged particles, such as protons, deuterons, alpha-particles and light ions, allow the depth dose distribution to be radically improved. Unlike the electron-photon radiation, beams of heavy charged particles undergo much weaker scattering as they penetrate deeper and deeper in tissues. They have well defined ranges, linear energy transfers (LET) of these particles increase with the penetration depth forming the so-called "Bragg peak" at the end of the range, which may make the dose absorbed in the deep focus several times greater than on the surface of the body even at irradiation from the same direction.

It should be mentioned that dose fields of heavier relativistic nuclei, such as neon or argon, are formed to an appreciable extent by secondary particles arising from heavy ion fragmentation processes, which results in an undesirable dose contribution behind the Bragg peak.



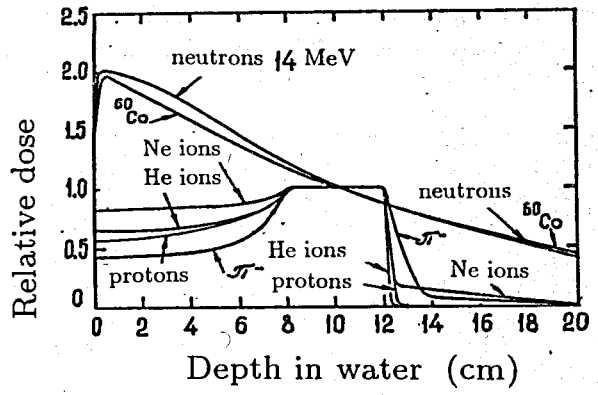
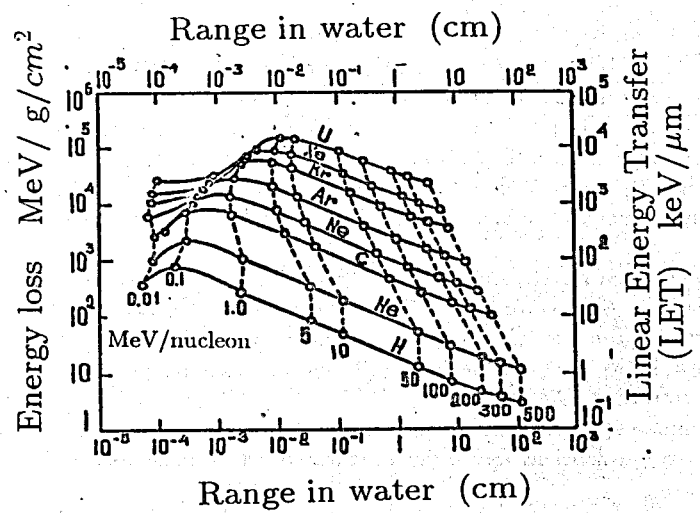



Fig. 2. Depth dose distributions for beams of heavy charged particles, $^{60}Co$ gamma-rays and 14-MeV neutrons [6].




Fß. 3. Dependence of LET on the range of heavy charged particles in $H_2O$ [8].

In Fig. 2 [6] depth dose distributions of heavy charged particles ,$^{60}$Co gamma-rays and 14-MeV neutrons are compared. The energy spectrum of the heavy charged particle beams is selected so as to produce a uniform dose distribution at a depth from 8 to 12 cm in tissue.

As is evident, thanks only to their advantage of geometrical factors of the absorbed dose distribution, heavy charged particle beams allow 2–3 times lower exposure of normal tissues around the tumour as compared with the $^{60}$Co gamma-rays. As a result, they can be more effective for irradiation of deep-lying large tumours located near vital organs.

Apart from distinct advantages of the geometric, also called macroscopic, absorbed dose distribution, the heavy charged particles are characterized by advantageous changes in some factors of biological effect related to high values of linear energy transfers (LET) or features of microscopic absorbed dose distribution. For gamma-rays and electrons, only a small part of the absorbed dose is deposited at LET up to 30 keV/$\mu$m [7]. For protons, alpha-particles and heavier ions the relationship between LET and the particle range in $H_2O$ is shown in Fig. 3 [8]. The high-energy region of the LET spectrum extends as far as 10 keV/$\mu$m for protons, 250 keV/$\mu$m for helium ions, 1500 keV$\mu$m for neon ions. For the neutron beam [9] and for the beam of negative pi-mesons in the dose peak region [10] the LET spectra extend up to 90 keV/$\mu$m.

In a wide interval of high LET energies beams of heavy charged particles are characterized by increased relative biological effectiveness (RBE), which is defined for this type of radiation as a ratio between the dose of 200-keV gamma-rays producing a certain biological effect and the of the radiation in question producing the same effect. According to the current concepts, death of cells exposed to a low-RBE radiation usually arises from accumulation of sublethal damages, which are easily repaired individually. The high-RBE radiation kills cells causing single irreversible damages.

A tumour often has oxygen-deficient regions which are less sensitive to the low-RBE radiation. A measure of this difference is the oxygen ratio (OR) defined as a ratio between the dose necessary for producing a certain biological effect (e.g a 50% survival level) in oxygen-deficient cells and the dose producing the same effect in oxygen-saturated cells.

For gamma-rays and electrons the OR is 2.5–3. The high-LET radiation interacts with oxygen-deficient and oxygen-saturated cells almost identically, and the OR decreases.

Figure 4 displays the experimental data on the dependence of the RBE and OR on LET [11]. In region I of LET values from 1 to 10 keV/$\mu$m the RBE is at its minimum and close to 1. In region II (10–100 keV/$\mu$m) the RBE increases to its maximum and in region III (over 100 keV/$\mu$m) it again decreases because of saturation effects. The OR is at maximum in region I, smoothly decreases in region



II and reaches its minimum value 1 in region II at LET about 200 keV/$\mu$m. Apart from the advantageous changes in these two factors (increasing RBE and decreasing OR), the biological effect of high-LET heavy charged particles is also characterized by smaller dependence on the cell cycle phase and fraction conditions as compared with a low-LET radiation [12, 13].

As was shown in [6, 14], one could expect that this difference in the factors of biological effect between the low-LET and high-LET densely ionizing radiations would increase the damaging effect on the tumour while the damage of normal tissues inside the tumour volume would be kept at the same level.

The relationship between the dose and the tumour damage probability is characterized by a very steep curve: an increase of 10–20% in the dose leads to an increase from 20 to 80% in the healing efficiency [15]. With rare-ionizing radiation, the therapeutic interval is often very narrow, Fig. 5 [2]. At the healing probability of 80% the complication probability is as high as 30%.

Even if all advantageous changes in the biological factors of high-LET heavy charged particles only double the therapeutic ratio, then, as follows from Fig. 5, the complication probability can be practically reduced to zero while the healing probability remains as high as 80% [2].

As compared with the currently used gamma-radiation, all heavy charged particles have similar advantages as far as pure geometrical factors of dose distribution are concerned. Fast neutrons do not have depth dose distribution advantages, but they may be more effective against resistant tumours owing to favourable biological factors stemming from high LET. If only the geometrical factors of dose distribution are taken into consideration, protons and light ions will be the best for radiotherapy. If clinical trials prove the advantage of neutrons in treating resistant tumours, then heavy ions, combining the advantageous features of physical and biological factors, will be the most promising for radiotherapy.

Recently some investigations have shown that a small admixture (10–20%) of high-LET radiation causes a disproportionately strong decrease in the OR (from 2.5 to 1.8–1.5) [16, 17, 18]. Therefore combination of low-LET and high-LET radiation, e.g. high-energy proton and neutron beams, can be greatly promising.

## 4. Initial period of clinical trials with heavy nuclear particle beams

The idea of using heavy charged particles in radiotherapy was put forward by R.Wilson as far back as 1946 [19], but its implementation became possible only after heavy charged particle accelerators in the range of hundreds of MeV had appeared.

In 1952 Tobias and Lawrence [20] were the first to use the proton, deuteron and alpha-particle beams from the synchrocyclotron in Berkeley (USA) for medical and biological research. In 1956 Larsson [21] began similar investigations with 187-MeV

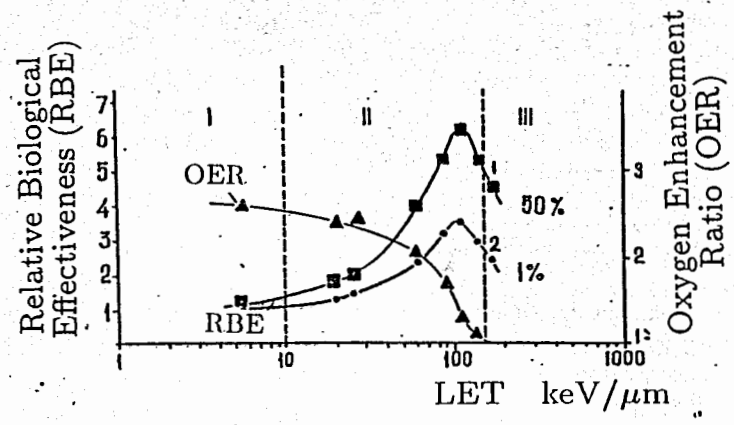



Fig. 4. Experimental dependence of RBE and OR on LET [11].

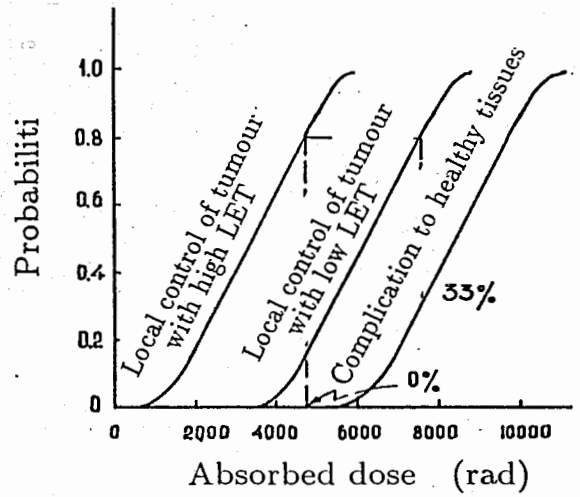



Fig. 5. Tumour healing probability for radiation with low and high LET and the probability of complications in normal tissue as a function of the dose [2].



protons in Sweden. Clinical research on using high-energy protons in radiotherapy were carried out by Kielberg at the 160-MeV synchrocyclotron of Harvard University (USA) since 1959 [22].

Up to date 26 centres in the world have used or keep using heavy charged particles for radiation treatment. In all of them, except Loma Linda (USA) and Chiba (Japan), radiotherapeutic heavy charged particles are produced in physics research accelerators for it reduces the total cost of wide clinical research by many times. Another 19 centres like this are supposed to be established in the coming years. The data on all these centres are given in Tables 3 and 4 [23]. About 20,000 patients have been treated with heavy charged particles in the world. However the maximum experience and the best results are concentrated in two comparatively narrow fields of ophthalmoncology and intracranial target irradiation. For example, in 1991 all patients treated with protons 66% were treated for an eye tumour and 17% for an intracranial tumour [24].

In the Laboratory of Nuclear Problems the original task was as wide as to obtain medical beams from the operating accelerator to treat tumours of different locations.

The first proton beam in the Soviet Union (now CIS) that possessed parameters required of radiotherapy was produced on V.P.Dzhelepov's proposal in the 680-MeV phasotron at the Laboratory of Nuclear Problems of JINR (Dubna) in 1967 [25]. The research with this beam was carried out by a groups of physicists from the Laboratory of Nuclear Problems in collaboration with the scientists from Institute for Experimental and Clinical Oncology of the USSR Academy of Medical Sciences (now the Cancer Research Centre of the Russian Academy of Medical Sciences—CRS RAMS). Clinical investigations began after a series of physico-dosimetric and radiobiological investigations. They were carried out with the medical proton beam at the LNP JINR in the years 1968 to 1974 (suspended for the accelerator conversion and construction of a multiroom clinico-physical complex).

During this initial period of clinical trials with the medical proton beam at the LNP JINR 84 patients underwent radiation treatment mainly for malignant tumours of the oesophagus and lungs [26]. The proton beam was available for medical purposes 2 times a week. Each patient was irradiated by fractions (10–15 sessions for 1–1.5 months), the total number of treatment sessions amounting to about a thousand. In this period the multifield irradiation was replaced by rotation irradiation, the dose distribution maximum (Bragg peak) automatically brought into coincidence with the tumour.

As a result of the initial research stage, the correctness of the basic physico-technical, radiobiological and clinical prerequisites was proved, irradiation techniques were devised for certain specific tumour sites, usefulness of extending the clinical research on proton therapy of malignant tumours was shown.

Table 3. Worldwide charged particle patient totals [23]
January 1996

| WHO | WHERE | WHAT | DATE FIRST RX | DATE LAST RX | RECENT PATIENT TOTAL | DATE OF TOTAL |
|---|---|---|---|---|---|---|
| Berkeley 184 | CA. USA | p | 1954 | – 1957 | 30 | |
| Berkeley | CA. USA | He | 1957 | – 1992 | 2054 | June–91 |
| Uppsala | Sweden | p | 1957 | – 1976 | 73 | |
| Harvard | NA. USA | p | 1961 | | 6626 | Jan–96 |
| Dubna | Russia | p | 1967 | – 1974 | 84 | |
| Moscow | Russia | p | 1969 | | 2877 | May–95 |
| Los Alamos | NM. USA | $\pi$- | 1974 | – 1982 | 230 | |
| St. Petersburg | Russia | p | 1975 | | 969 | Dec–95 |
| Berkeley | CA. USA | heavy ion | 1975 | – 1992 | 433 | June–91 |
| Chiba | Japan | p | 1979 | | 86 | June–93 |
| TRIUMF | Canada | $\pi$- | 1979 | – 1994 | 367 | Dec–93 |
| PSI (SIN) | Switzerland | $\pi$- | 1980 | – 1993 | 503 | |
| PMRC, Tsukuba | Japan | p | 1983 | | 462 | July–95 |
| PSI (SIN) | Switzerland | p | 1984 | | 1785 | Dec–94 |
| Dubna | Russia | p | 1987 | | 39 | July–95 |
| Uppsala | Sweden | p | 1989 | | 65 | Spring–95 |
| Clatterbridge | England | p | 1989 | | 656 | Dec–95 |
| Loma Linda | CA. USA | p | 1990 | | 1262 | April–95 |
| Louvain-la-Neuve | Belgium | p | 1991 | | 21 | Nov–93 |
| Nice | France | p | 1991 | | 636 | Nov–95 |
| Orsay | France | p | 1991 | | 673 | Nov–95 |
| N.A.C. | South Africa | p | 1993 | | 106 | Dec–95 |
| IUCF | IN. USA | p | 1993 | | 1 | Dec–94 |
| UCSF–CNN | CA. USA | p | 1994 | | 50 | Oct–95 |
| HIMAC, China | Japan | heavy ion | 1994 | | 55 | Aug–95 |
| TRIUMF | Canada | p | 1995 | | 5 | Dec–95 |
| | | | | | 1100 pions | |
| | | | | | 2542 ions | |
| | | | | | 16506 protons | |
| | | | | TOTAL | 20148 all particles | |

## 5. Multiroom complex at the Laboratory of Nuclear Problems

To fulfil the research programme, a multiroom clinico-physical complex [27, 28] was built at the Laboratory of Nuclear Problems by the end of 1985. Now the complex comprises five medical proton channels for exposure of deep-lying tumours to wide and narrow proton beams of different energy (from 70 to 660 MeV), a medical $\pi$-meson channel for treatment with intense negative $\pi$-meson beams of energies from 30 to 80 MeV, a medical neutron channel (the average neutron energy in a beam is about 350 MeV) to irradiate large radioresistant tumours, a gamma therapy unit used as a back-up radiation source and for distant gamma treatment in combined treatment methods. The general view of the clinico-physical complex and phasotron beam channelling are shown in Figs. 6 and 7.

Channel VIII is used to shape wide (diameter 3-6 cm) proton beams of energies 100, 130 and 200 MeV and to supply them to rooms 1 and 2 [28–30]. This channel



Table 4. Proposed "New facilities for proton & ion beam therapy" [23]
December 1995

| INSTITUTION | PLACE | TYPE | 1ST RX? | COMMENTS |
|---|---|---|---|---|
| P.S.I. | Switzerland | p | 1995 | 200 MeV, var. energy, gantry, dedicated line |
| Berlin | Germany | p | 1996 | 72 MeV cyclotron; eye treatment beam line. |
| G.S.I. Darmstadt | Germany | ion | 1996 | First Carbon beam in the medical cave 7/6/95 |
| KVI Groningen | The Netherlands | p | 1997? | plan:- 200 MeV accel.; 2 rms; 1 gantry; 1 fix. |
| NPTC (Harvard) | MA USA | p | 1998 | at MGH; 235 MeV cyclotron; gantry; 4 horiz beam |
| NC Star | NC USA | p | 1999? | cyclotron; 70-300 MeV; 2 horiz; 1 gantry |
| Regensburg | Germany | p | 1999? | gantry; 1 fixed beam; 1 eye beam. |
| Hyogo | Japan | ion | 2000 | protons & ion; 2 gantries; 1 horiz; 1 vert; 1 45°deg. |
| TERA | Italy | ion | 2000? | $H^-$ accel; 60-250 MeV p; +BNCT; isotope prod. |
| AUSTRON | Austria | ion | ? | protons and light ions. |
| Beijing | China | p | ? | 250 MeV synchrotron. |
| Brookhaven | NY USA | p | ? | linear accelerator. |
| Clatterbridge | England | p | ? | upgrade using booster linear accelerator. |
| ITEP Moscow | Russia | p | ? | 3 horiz. -1 fix beam, 2 gantry, 1 exp., $H^-$ accel. |
| Jülich (KFA) | Germany | p | ? | exp. beam line; plans for therapy. |
| Krakow | Poland | p | ? | 60 MeV proton beam. |
| Kyoto | Japan | p | ? | 250 MeV synchrotron; gantry; 1 fixed horiz beam. |
| Proton Development N.A. Inc. | IL USA | p | ? | 300 MeV protons; therapy & lithography |
| Kashiwa | Japan | p | ? | no details yet; will start construction in 1996 |

also allows a diagnostic (diameter about 3 mm) proton beam of 660 MeV to be shaped in room 1 for proton tomography [31, 32]. Channel XI is intended for shaping a narrow (diameter 5–20 mm) 660-MeV proton beam in room 3 [33]. To produce a medical $\pi$-meson beam, extracted protons are transported by channel IX to a wide angle magnetic lens, which vertically focuses the negative $\pi$-mesons produced in the target and supplies them up to room 4 [34–37]. Channel X serves to shape a medical neutron beam in room 5 [38, 39] and a wide proton beam with an irradiation field up to 21 cm in diameter. Channel VI is used to shape a narrow proton beam of energies ranging from 70 to 100 MeV.

## 6. Radiation treatment and diagnosis equipment

As pointed out in Sec. 3, the dose distribution for heavy charged particles is substantially better than for gamma – quanta and electrons, which allows flexible

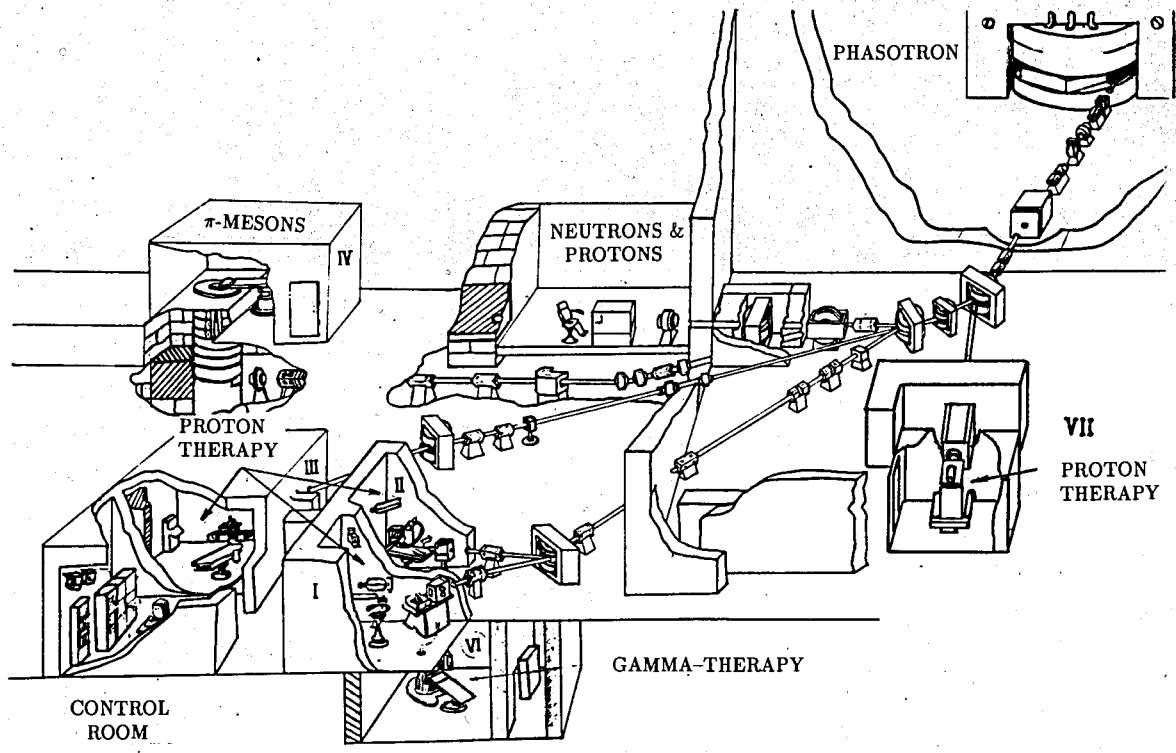



Fig. 6. Multiroom complex for heavy charged particle treatment at the JINR phasotron.



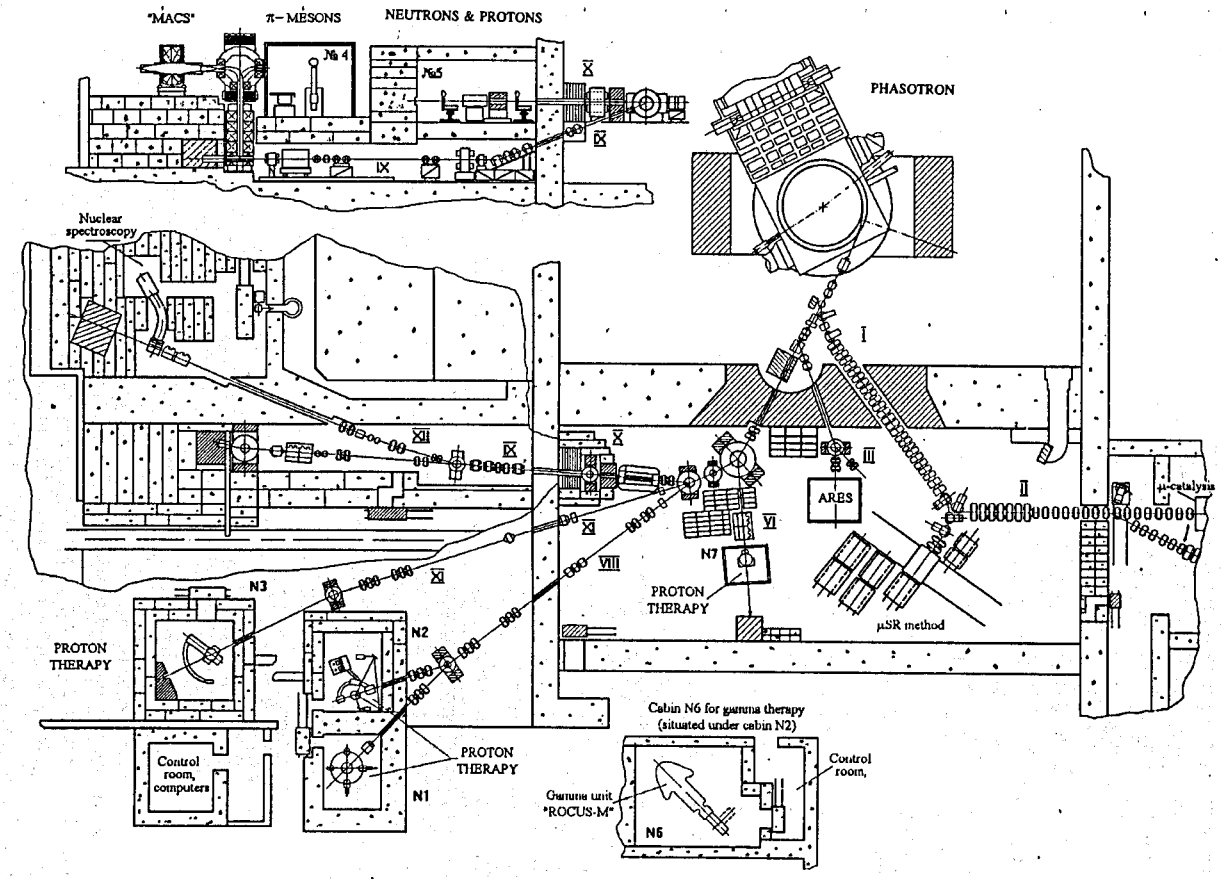



Fig. 7. LAYOUT OF PHASOTRON BEAM CHANNELS AT THE LABORATORY OF NUCLEAR PROBLEMS, JINR

control to meet different clinical requirements or criteria. To employ this important advantage of heavy charged particles in full measure, one needs universal methods to form dose fields and instruments to measure them, methods for precise localization of a tumour in the patient's body, and adequate methods to control coincidence of the dose maximum with the tumour. In the Laboratory of Nuclear Problems investigations have been carried out to meet these requirements.

Monoenergetic beams of heavy charged particles are rather rare tools in clinical practice because the size of the focus to be irradiated is, as a rule, noticeably larger than the Bragg peak. To increase the width of the maximum dose region, a nonmonochromatic beam with a specially selected spectrum is used, which is equivalent to superimposing several Bragg curves of different penetration, Fig. 8 [40].

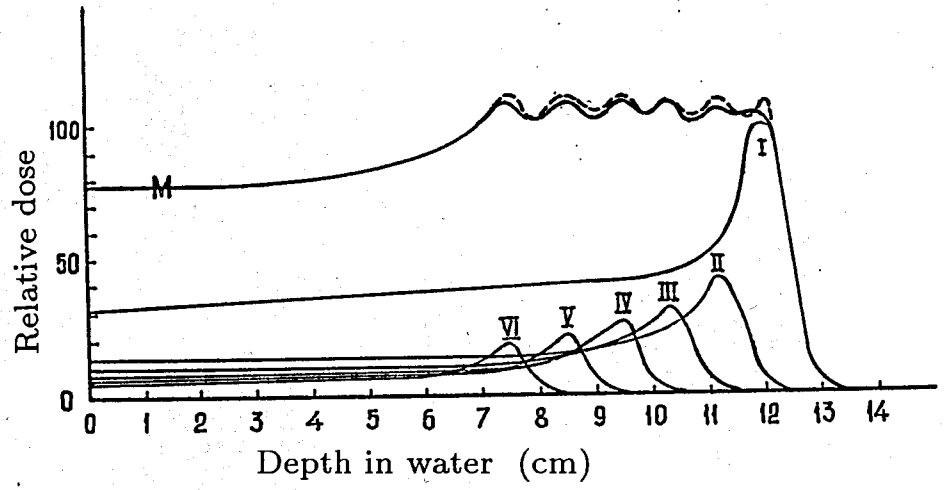



Fig. 8. Principle of formation of a depth dose distribution with a wide maximum and a steep back edge. The energy and intensity of individual monochromatic proton beams is selected such that their mix yielded a modified Bragg curve with the dose maximum about 5 cm wide [40].

Ion optics can be used to form the required dose distribution for nonmonochromatic beams of heavy charged particles resulting from deceleration of the extracted primary beam or from interaction of the primary beam with the target. In one of the methods, proposed and tested at the Laboratory of Nuclear Problems, an



automated collimator system isolates only that part of the wide particle energy spectrum which is necessary for formation of a modified spread-out Bragg curve with a steep back edge, Fig. 9 [30].

That dose fields of practically any space configuration can be formed with heavy charged particles is only helpful if the shape and size of a tumour as well as its location in the patient's body are determined fully enough.

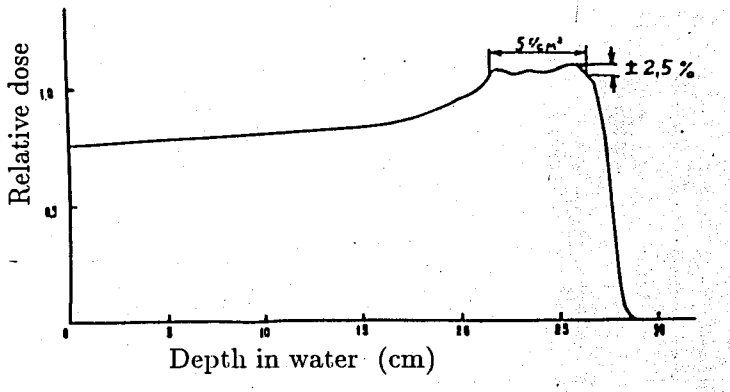



Fig. 9. Modified spread-out Bragg curve.

Conventional methods of topical X-ray diagnosis do not allow the accuracy required of heavy charged particle therapy. An important step in this direction was application of computer X-ray tomography methods. In the Laboratory of Nuclear Problems a simple X-ray computer tomograph is developed to get topometric information while the patient is in the same position as in the coming treatment session [53]. In Fig. 10 there is a reconstructed tomographic image of the patient's chest, obtained with this apparatus, and dose fields produced by a proton beam in rotation irradiation.

With proton computer tomography methods, all heterogeneities and variations of the tissue depth in any direction of the heavy particle beam can be precisely determined in terms of the path of these particles without cumbersome calculations typical of X-ray tomography, or by calibrating them against proton tomograms, and thus an individual programme can be worked out for multifield rotation or scanning irradiation of a patient. A version of this device is developed at the Laboratory of Nuclear Problems [31, 56]. Figure 11 displays a tomographic image of the phantom human chest obtained with this device.

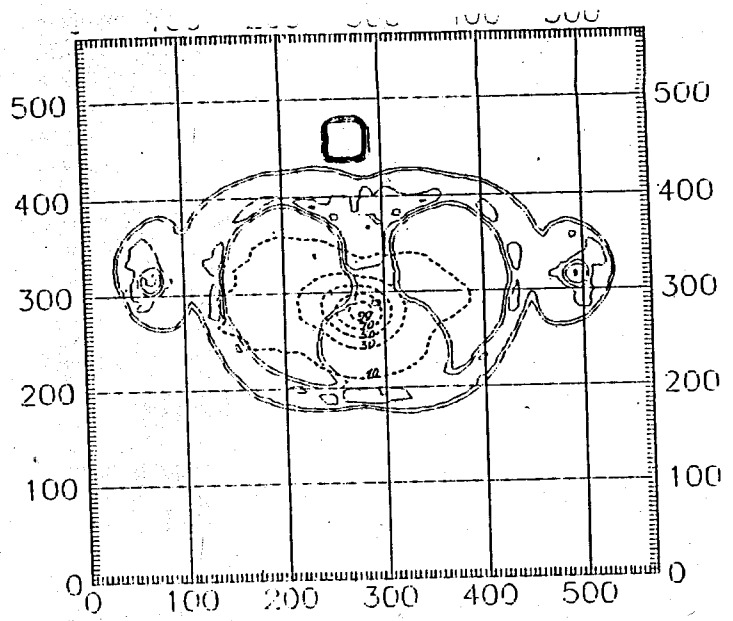



Fig. 10. X-ray tomogram of the patient's chest with dose fields produced by a 200-MeV proton beam in rotation irradiation of the oesophagus tumour.

Accurate coincidence of the formed dose distribution with tumour volume during irradiation is a very complicated problem that is not completely solved so far. The first step in this direction was made at the Laboratory of Nuclear Problems of JINR in co-operation with the CRC RAMS [57, 59]. In the case of the oesophagus tumour a miniature semiconductor transducer is introduced in the oesophagus. Signals of the transducer are used by the feedback system for automatic control of the proton beam energy and compensation for all changes in heterogeneity and depth of the tumour at each small change in the position of the patient in the course of rotation.



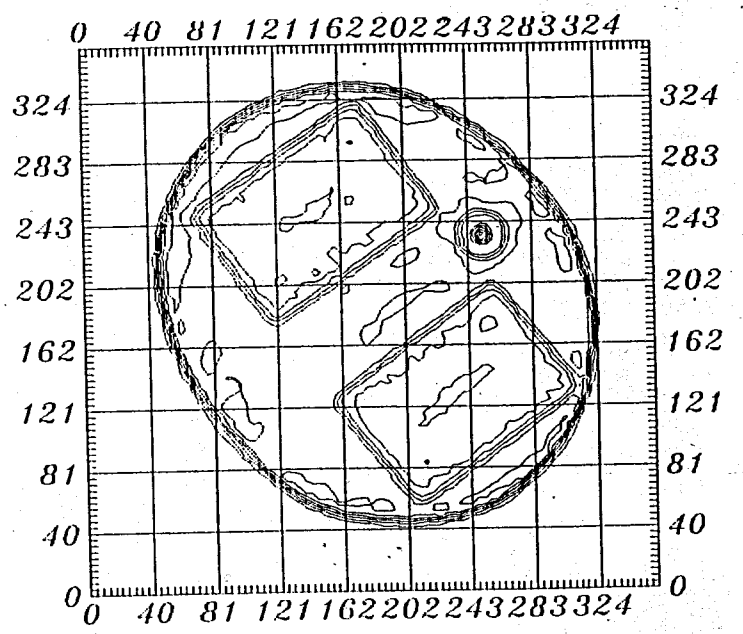



Fig. 11. Reconstructed image of the phantom human chest obtained with the proton computer tomograph.

The accuracy of coincidence of the dose maximum with the tumour also depends on some clinical factors, first of all on the accuracy of specifying the minimum treatment volume, which consists of the tumour itself and surrounding tissues irradiated to ensure damage of all malignant cells. Besides one should take into account the uncertainty of the patient's positioning in the beam from session to session, the degree of his immobility during the session, variation in the shape and position of internal organs, etc. To solve all these problems, it is necessary to accumulate

and generalize clinical data, to devise methods for rigid fixation of patients, to develop precision systems for X-ray and optical centering of the patient to control his position at the positioning and treatment stages.

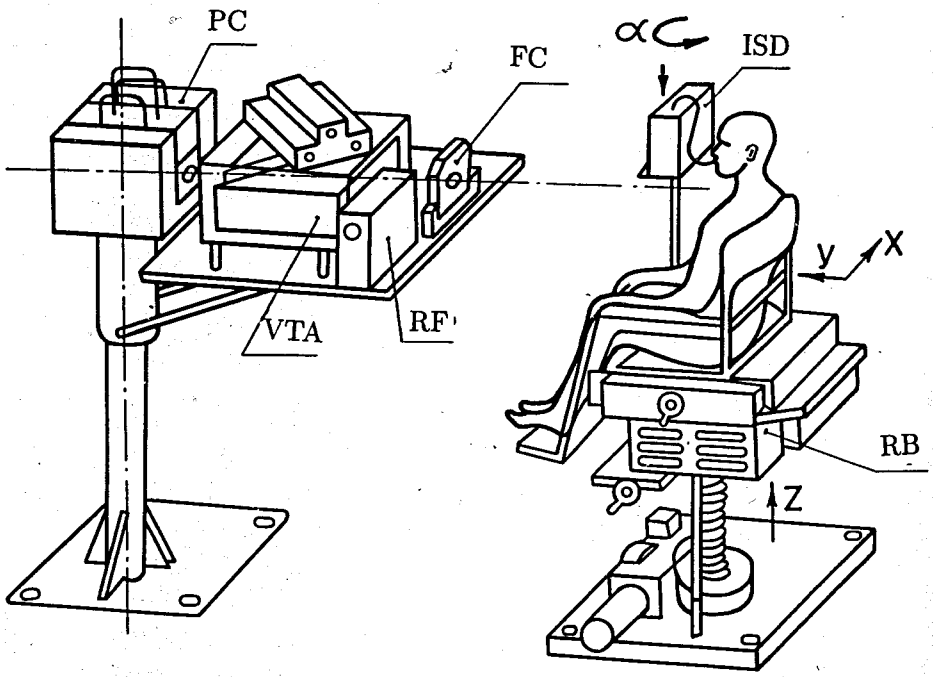



Fig. 12. Device "Meson" for scanning rotation irradiation of deeply lying tumours. PC—principal collimator, FC—final collimator, VTA—variable-thickness absorber, RF—ridge filter, RB—rotating bench, ISD—intracavity semiconductor detector, X, Y, Z, $\alpha$—position coordinates for the rotating bench chair.



A device "Meson" for scanning rotation irradiation of deeply lying tumours, allowing for the above requirements, is developed at the Laboratory of Nuclear Problems in co-operation with the CRC RAMS. Its general view is shown in Fig. 12 [52].

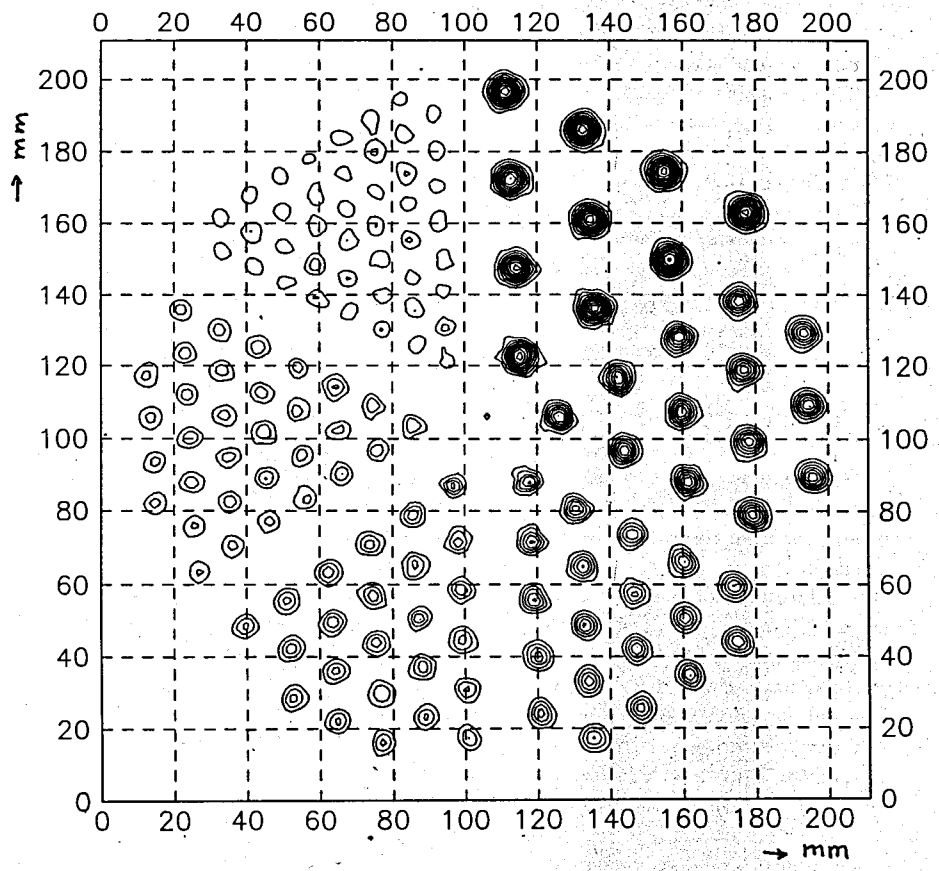



Fig. 13. A tomogram of a plexiglass phantom in the form of $^{22}$Na isotope concentration levels obtained with the positron emission tomograph. Round holes in the phantom (clockwise) are 2,5; 3,0; 3,5; 4,0; 5,0 and 6 mm in diameter.

The first home-produced full-scale positron emission tomograph (PET) consisting of 512 composite scintillators and 256 photomultipliers has been constructed at the Laboratory of Nuclear Problems. The composite scintillators are the main feature of the PET. They combine small scintillation time (about 3 ns) and quite a high recording efficiency for annihilation gamma-quanta ($\sim 45\%$) at the time resolution 1.7 ns. Each scintillator is assembled from 160 alternating layers of plastic scintillator and lead foil 150 $\mu$m and 30 $\mu$m thick respectively.

The first tests were carried out and some characteristics of the tomograph were measured using positron emitters. Figure 13 shows a tomogram of a plexiglass phantom in the form of $^{22}$Na isotope concentration isolevels obtained with this PET. The spatial resolution obtained was 4.0 mm (FWHM) in the ring plane and 10.5 mm along the axis of the tomograph. These parameters compare well with the majority of foreign-made commercial PETs. On the other hand, composite scintillators and some other design features allowed the cost of the tomograph to be a few times ten lower than that of foreign commercial PETs. The PET will be used for scientific research and diagnosis purposes and to verify the irradiation of cancer patients undergoing radiation treatment with medical beams of the JINR phasotron.

## 7. Physical and dosimetric measurements

Special detecting equipment has been designed, constructed and installed, running on line with the computer, mainly in the automatic mode, to gain physical and dosimetric information on the medical beams and to tune the particle channels. Its constituent parts are ionization chambers to monitor primary and secondary beams [41], calorimeters for absolute calibration of the primary proton beam [42, 43], ionization chambers to measure the proton beam profile, fixed and movable rulers of semiconductor elements for detailed measurement of transverse distribution of charged particle beams [44], an isodosegraph to determine space distribution of charged particle beams in the air and water [45], magnetic induction sensors to monitor the proton beam in vacuum [46], vacuum profilometers and optical indicators to monitor the beam shape and position in vacuum, scintillation and semiconductor counters to measure the beam composition, etc.

With this equipment the parameters of the extracted proton beam from the JINR phasotron were measured [38, 39] and all necessary physical and dosimetric characteristics of the medical beams were obtained. The main results of the measurements are shown in Figs. 14–16 and summed up in Table 5.

The absolute accuracy of the dosimetric measurements was $\pm 5\%$ for the proton beams and $\pm 2\%$ for the gamma unit ROKUS-M [47–51].



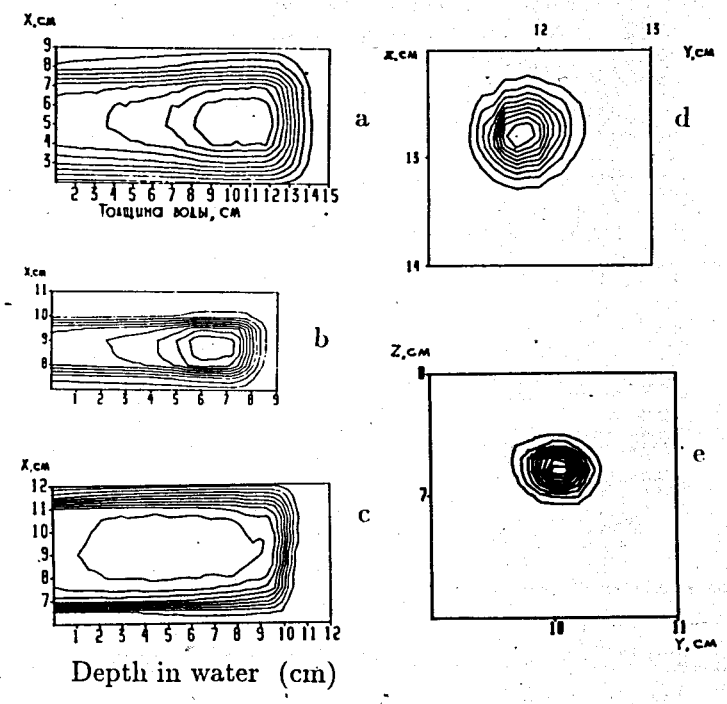



Fig. 14. Examples of isodose distributions for 200, 100 and 130 MeV proton beams (a, b, c) and transverse isolevels of narrow proton beams (**d**, e) provided by the isodosegraph with a miniature silicon detector.

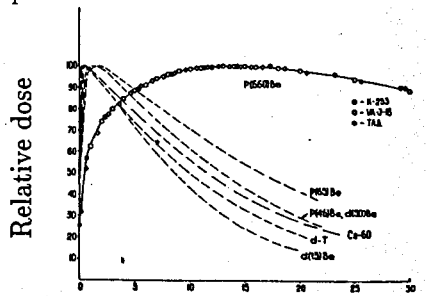



Fig. 15. Depth dose distribution of the neutron beam arising from collision of 660-MeV protons with a beryllium target 36 cm thick
(solid curve; points of different form on it correspond to indications of different detectors). Dashed curves are the data from other investigations at lower neutron energi

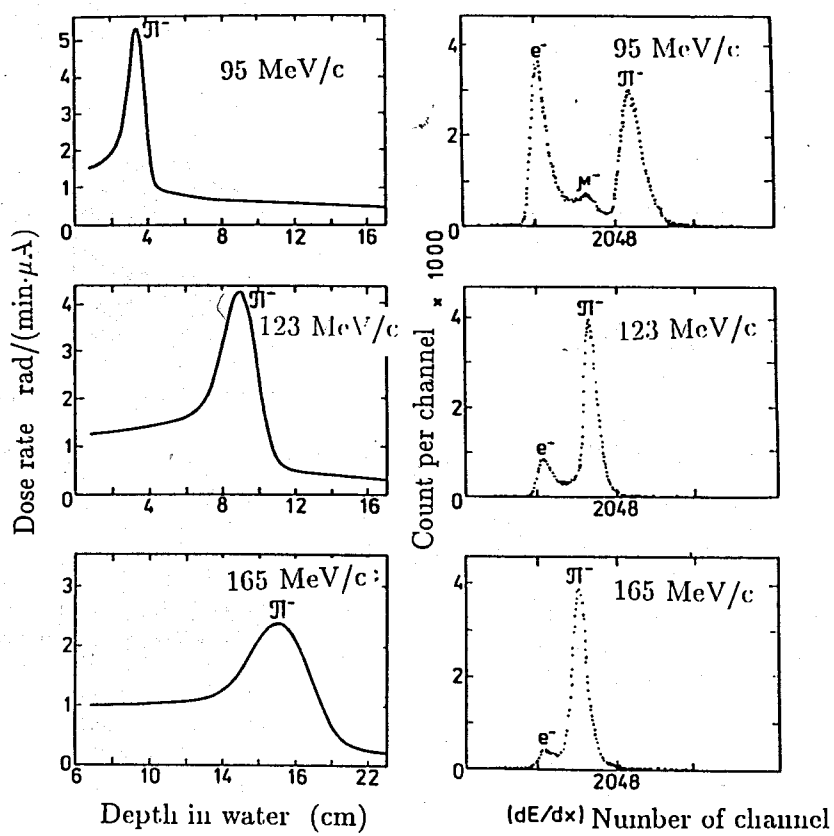



Fig. 16. Examples of depth isodose distributions and compositions of meson beams of different energies obtained with the isodosegraph and scintillation counters.



Table 5. Physical and dosimetric characteristics of medical beams from the converted phasotron for the extracted proton intensity 1 μA

| Channel number | Energy of transported protons (MeV) | Room number | Type and energy of particles in room | Particle intensity in room ($s^{-1}$) | Beam diameter in room (cm) | Dose rate at irradiation site (rad/min) | Remarks |
|---|---|---|---|---|---|---|---|
| VIII | 200 | 1 | protons 200 MeV | $5 \cdot 10^8$ | 2–6 | 10–200 | 200 MeV protons are produced by deceleration in carbon moderator |
| VIII | 100 | 1 | protons 100 MeV | $10^8$ | 2–6 | 30–120 | 100 MeV protons |
| VIII | 660 | 1 | protons 660 MeV | $10^6$ | 0,3 | 6,0 | For diagnosis purposes |
| VIII | 130 | 2 | protons 130 MeV | $2 \cdot 10^8$ | 3–6 | 25–100 | 130 MeV protons are produced by deceleration in carbon moderator |
| XI | 660 | 3 | protons 660 MeV | $5 \cdot 10^7$ | 0,5–2 | 600 | For intracranial irradiation |
| IX | 660 | 4 | $\pi^-$ mesons 30-80 MeV | $(1 \div 2) \cdot 10^7$ | 2–10 | $4 \div 6$ | π-mesons are produced on a tungsten target 5 cm thick |
| X | 660 | 5 | neutrons average energy 350 MeV | $(3 \div 5) \cdot 10^8$ | 5–15 | $2,5 \div 9 \cdot$ | Neutrons are produced on a beryllium target 36 cm thick |
| X | 250 | 5 | protons 250 MeV | to $5 \cdot 10^9$ | to 21 | to 2000 | 250 MeV protons are produced by deceleration in carbon moderator |
| VI | 70-100 | 7 | protons 70-100 MeV | $(1 \div 3) \cdot 10^8$ | 0,5–2 | to 3000 | 70–100 MeV protons are produced by deceleration in carbon moderator |

## 8. Treatment rooms

The clinico-physical complex in the Laboratory of Nuclear Problems of JINR has seven treatment rooms specially equipped for medico-biological and clinical investigations. Four rooms (1, 2, 3, 7) are intended for proton therapy, room 4 for negative π-meson therapy, room 5 for neutron therapy and treatment with large-field proton beams. Room 6 houses a gamma therapy unit ROKUS-M.

In room 1 there is unique physical and medical equipment running on line with

the computer. The equipment allows irradiation of large, deeply lying tumours of a complicated shape, such as malignant tumours of the oesophagus, lung and neck [52].

Special versions of the horizontal X-ray computer tomograph [53] and proton computer tomograph [313, 32] have been designed for room 1. Both units are linked to the rotating bench where a patient is seated during proton treatment. Thus it is possible to get diagnostic computer tomograms and to expose the patient to protons in the same position, which allows the treatment to be planned and carried out with high accuracy.

For irradiation, and original method of rotation three-dimensional scanning with the Bragg peak (the dose maximum at the end of the proton beam range) is used [59]. The patient, fixed in the sitting position in the chair of the rotating bench, is slowly rotated in the horizontal proton beam. A computerized system keeps track of the bench rotation angle and automatically adjusts the beam energy (i.e. the particle range) so that the Bragg peak always coincides with the tumour in any beam direction. This allows the maximum dose to be focused on the tumour and the exposure of the surrounding normal tissues to be reduced.

The computer calculates the irradiation programme from the computer tomograms obtained for the patient at the same horizontal level immediately before the proton treatment (when the patient is already fixed in the chair), Fig. 17. The rotation irradiation is carried out layer by layer, the chair being discretely moved along the rotation axis. The method provides a high accuracy of irradiation, allows the introduction of intracavity dosimetric sensors to be avoided, and does not require reproducibility of the patient's position in the sessions of the fractionated treatment.

Room 2 is intended for treatment of gynaecological tumours with a wide proton beam. The depth dose distribution is formed by a ridge filter. Regional lymph nodes are additionally irradiated on the gamma unit in room 6.

Room 3 for proton therapy contains the equipment for stereotactic convergent irradiation of small intracranial targets with a narrow 660-MeV proton beam by the "shoot-through" technique.

Room 4 is equipped for irradiation of patients in the supine position. A beam of negative $\pi$-mesons is delivered here. After termination of the radiobiological experiments this beam will be used for clinical research on treatment of malignant nasopharynx, mouth, thyroid and salivary gland tumours, etc.

Room 5 accommodates a therapeutic neutron beam to be used, both independently and in combination with the proton beam, for treatment of large hypoxic tumours.

A wide 250-MeV proton beam is also supplied to this room for simultaneous rotation-scanning irradiation of large, deeply lying tumours of a complicated shape.

For each of the beams (protons and neutrons) an individual rotating bench is



used for rotation irradiation of patients in the sitting position.

The simultaneous proton irradiation technique resembles the rotation-scanning irradiation, but the available unparalleled equipment allows simultaneous irradiation with 14 narrow horizontal independent proton beams. Horizontal layers exposed to each of the narrow beams are joined vertically so that the total maximum height of the target is 21 cm.

Room 7 accommodates a proton beam of energy 70–100 MeV and dose rate several thousands of rad/min, enough to irradiate eye tumours for about 1 min. A bench for treating patients in the sitting position is installed here.

To date all beam channels have been adjusted and all necessary physical and dosimetric characteristics of the medical beams have been measured. In 1987–1989 radiobiological experiments were carried out with high-energy proton and neutron beams and proton treatment of patients began (in collaboration with the CRC RAMS), using the devised techniques of dose field formation, rotation-scanning irradiation of deeply lying tumours, and the new methods of reconstructive X-ray tomography whose novelty is confirmed by inventor's certificates [55–57]. By the end of 1995 a total of 39 patients underwent fractionated treatment with medical beams from the converted phasotron.

## 9. Clinical results

Radiotherapy is the main treatment of uterine cervix cancer. For almost 75% of patients it is not only the main but also the sole treatment. Yet, despite steady progress of radiotherapy 30–44% of cervix cancer patients die of the disease within 5 years. Besides, 5–30% of patients develop radiation lesions of normal organs and tissues, predominantly of the rectum and bladder, in various periods after treatment. In this connection, it is still of great importance to increase the effectiveness of radiation treatment of uterine cervix cancer.

With traditional treatment (intracavity gamma irradiation of the uterus), the 5-year survival was 63.5–85% (for all stages of the disease), and the radiation-induced complications in normal organs adjacent to the uterus were observed in 6.5–27.3% of patients.

New types of ionizing radiation—heavy charged particles of high energy, in particular protons—have come into use to increase the effectiveness of radiation treatment of uterine cervix cancer, to optimize the dose distribution in the volume under irradiation, and to reduce radiation-induced complications in tissues and organs adjacent to the uterus.

Since December 1987 a total of 34 cervix cancer patients have received proton-gamma treatment at the Laboratory of Nuclear Problems. Six of them were given presurgery treatment, 25 received an independent radical course of proton-gamma

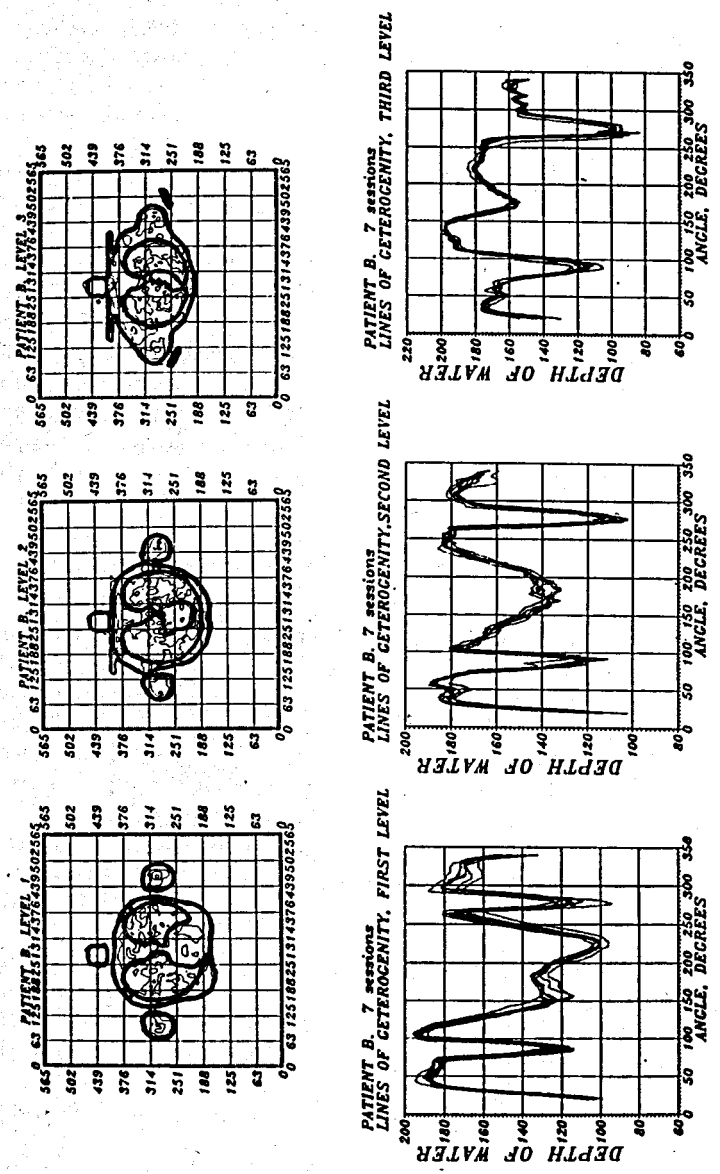



Fig. 17. Tomographic images of the patient's chest at three levels (top row) and treatment programmes (heterogeneity lines, bottom row) calculated from these tomograms for each fractionated treatment session.



treatment and 3 were treated palliatively.

The results of the combined proton-gamma treatment of uterine cervix cancer are presented in Table 6 [60]. A hundred per cent of the patients have been cured. Eighteen of the 34 patients have been followed up for over 3 and 5 years, 83% of them are alive showing no relapses or metastases. Three patients died of recurrent radioresistant disease, metastases to the upper third of the vagina (beyond the irradiation zone) and intercurrent disease (insult) 2 years after treatment.

Table 6. Results of proton-gamma treatment of uterine cervix cancer (CRC and LNP JINR)

| Stage | Number of patients | Cured | Alive without relapse or metastases over | | Died of | | |
|---|---|---|---|---|---|---|---|
| | | | 3 years | 5 years | relapse | metastases | intercurrent disease |
| IB | 11 | 11 | 10 | 5 | – | 1* | – |
| IIA,B | 4 | 4 | 3 | – | 1 | – | – |
| IIIB | 3 | 3 | 2 | – | – | – | 1** |
| Total | 18 | 100% | 15/18(83%) | 5/6(83%) | 1 | 1* | 1** |

* Two years after treatment—of metastases to the upper third of the vagina (beyond the irradiation zone).

** Two years after treatment—of insult. .

Radiation-induced reactions and complications in normal organs (bladder and rectum) and tissues adjacent to the irradiated target (uterus) were not observed in all patients.

The direct and remote results of the proton-gamma treatment have revealed the advantages of protons over other types of radiation in treatment of uterine cervix cancer, namely the absence of radiation-induced damage of the normal organs (bladder and rectum) adjacent to the uterus.

After the rotation scanning irradiation technique was tested on phantoms [54], it was used to treat oesophagus cancer. Toward April 1994 five oesophagus cancer patients were treated, the horizontal X-ray computer tomograph being used to get tomographic images of the patient's chest at three irradiation levels [61]. These

tomograms were taken during the entire course of fractionated radiation treatment for each patient, thus allowing all features of the patient's set-up to be taken into account. This group of patients is still to be followed up for 3 and 5 years after treatment to keep track of the clinical results. The Laboratory of Nuclear Problems of JINR is the first in the world to use the technique of rotation scanning irradiation with protons.

## 10. Prospects of using heavy nuclear particle beams for radiotherapy and diagnosis purposes at JINR

Apart from already available and tested beams of heavy nuclear particles from the phasotron of the Laboratory of Nuclear Problems, other basic facilities of JINR allow in principle beams like this to be used for radiotherapy and diagnosis purposes.

As far back as 1975 a possibility of using multicharged ion beams from the accelerating complex of the Laboratory of High Energies was examined [62]. To irradiate tumours up to 20 cm deep in the soft tissue one needs carbon and oxygen ion beams of energy about 400 MeV/nucleon and neon ion beams of energy about 500 MeV/nucleon. The intensity of these beams must be of the order of $10^{11}/Z^2$ nuclei/s. As pointed out in Sec. 3, these beams of multicharged ions may be quite promising for treating resistant tumours, which account for about 10% of all malignant formations [63].

In 1975 it was also proposed to use neutron beams from the reactors IBR-30 and IBR-2 in the Laboratory of Neutron Physics for medical and biological purposes [64]. It was shown that using filters one can in principle get beams of fast neutrons with the required energy distribution and adequate intensity. Also, the thermal neutron beams available from the IBR-2 reactor may be suitable for neutron capture therapy, in particular with boron-containing substances. This boron-neutron-capture therapy may be effective against some categories of brain tumours [63].

The effectiveness of radiation treatment greatly depends on the timely and accurate diagnosis. Prominent among cancer diagnosis methods is radionuclide diagnosis, especially its branch using ultrashort-lived positron-emitting nuclides.

There are concrete proposals and studies as to production of medical radionuclides at JINR's basic facilities, namely the JINR phasotron [65, 66] and the LUE-40 accelerator in the Laboratory of Neutron Physics [67]. Some diagnostic equipment for ion radiography and gamma introscopy based on proportional chambers has been developed at the Laboratory of High Energies [68]. However implementation of all these proposals and studies requires an adequate clinical basis in Dubna. For example, the medico-technical complex built in the Laboratory of Nuclear Problems is capable of providing several thousands of irradiation sessions a year or a full course of radiation treatment for 350 patients a year. Now, unfortunately, few patients are treated with the medical beams of the JINR phasotron because there



is no dedicated radiological hospital with the adequate number of beds and medical staff. As a result, the great investments in the scientific research of the problem and in construction of the medico-technical complex itself do not produce an adequate effect.

There arises quite an abnormal situation where there is sophisticated physical, technical and medical equipment already operational and no hospital, whose cost is less than a quarter of the investments made so far.

For the medico-technical complex to be effectively used, it is proposed to build a 60-bed specialized radiological hospital as part of medical department No 9 existing in Dubna. The radiological hospital is a seven-storeyed rectangular building 48 metres long by 15 metres wide, connected by passageways with the existing polyclinic and major hospital building of medical department No 9 for convenience of patients and medical staff. There is a design of the hospital made by the State Institute for Building Designs and approved by the experts.

The estimated investment is 4.0 million dollars, which includes only the cost of the most necessary equipment (at 1995 prices).

If the radiological hospital is built, about 3000 hours per year of the beam time will be required to provide a full course of radiation treatment for 350 patients. Now the cost of a treatment course for one patient is about 2000 dollars. The parallel use of the phasotron for physics experiments may reduce the cost of treatment to 1000 dollars. This is about an order of magnitude lower than in the projected hadron therapy centre in Italy [63].

## 11. Conclusion

A phasotron-based multiroom clinico-physical complex has been built and put into operation in the Laboratory of Nuclear Problems of JINR. It allows separate or combined treatment of cancer patients with wide and narrow beams of high-energy protons, negative pi-mesons and neutrons. This is the first such set of medical beams of heavy charged particles obtained at one accelerator. It allows the optimum selection of radiation for each patient based on dose distribution features and biological characteristics of each sort of particles as well as on the size and clinical features of the tumour.

Unique treatment and dose field formation techniques, new methods of reconstructive X-ray and proton tomography are developed and used. The world's first equipment is built and methods are proposed for rotation scanning irradiation of deeply lying tumours and for simultaneous scanning irradiation of a large target with several narrow proton beams, which ensures high accuracy and full computer control of the irradiation.

The projected construction of a 60-bed radiological hospital, prospects of using multicharged-ion and neutron therapy, the results of research on radionuclide pro-

duction and development of radionuclide diagnostic equipment at JINR open up possibilities of establishing an up-to-date treatment and diagnosis centre in Dubna, which will ensure extensive medico-biological and clinical research on tumour treatment with beams of heavy nuclear particles in the coming 10–15 years.

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