RADIOBIOLOGICAL RESEARCH WITH CHARGED PARTICLES BEAMS IN ITEP

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Abstract

Radiobiological researches with heavy ions have been started at ITEP in 2006 on unique heavy ion accelerating facility ITEP-TWAC. The main purpose of these researches is study of the biological efficiency of carbon ions for different types of biological objects, such as tumor and normal cells, in the framework of the development of heavy ion therapy for cancer treatment in Russia. Another possible area of application of this research is the space radiobiology, studying stochastic and deterministic effects of ionizing radiation in the space environment on human. In this work the experimental setup for radiobiological research with heavy ions in ITEP, the dosimetry system for dose measurements and the results of the radiobiological researches with carbon ions are presented.

INTRODUCTION

In the last few decades there is a tendency in the increasing of the number of hadron (protons and heavy ions) therapy centers, that are in general hospital-based facilities in versus the previous times when the treatments were performed in nuclear physics research centers. For today, hadron therapy in Russia is only represented by proton therapy, that is carried out in three scientific research centers in ITEP (Moscow), JINR (Dubna) and PNPI (Gatchina). Research in the field of carbon ion therapy is at the very beginning and currently several projects of the new facilities construction, mainly based on the particle accelerators for nuclear physics research, are under discussion.

In 1997 the project for the reconstruction of ITEP U-10 proton synchrotron (TWAC-ITEP project) was started. The aim of this project was to create new facility for heavy-ion acceleration up to relativistic energies and ion accumulation with energies up to several hundreds of MeV/u [1]. In 2004 realization of the first stage of the TWAC-ITEP project has been completed and as one of the results a possibility to accelerate and accumulate carbon ions C^{6+} with energy suitable for therapy application was shown [2]. After several years radiobiological research program with carbon ions was initiated in ITEP. Since then in collaboration with biophysicist and radiation oncologist from JINR and Russian Cancer Research Centre various kind of radiobiological experiments (surviving of irradiated cells, chromosome aberration, mutagenic influence of heavy ions) with cancer and normal cells, as well as with other types of biological systems have been carried out.

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EXPERIMENTAL SETUP

For radiobiological research at the TWAC-ITEP accelerator facility an experimental setup was organized at the end of the 511 beam-line (fast extraction beam-line from accelerator-storage ring U-10) in the building 120. Layout of the experimental setup is illustrated in Fig. 1

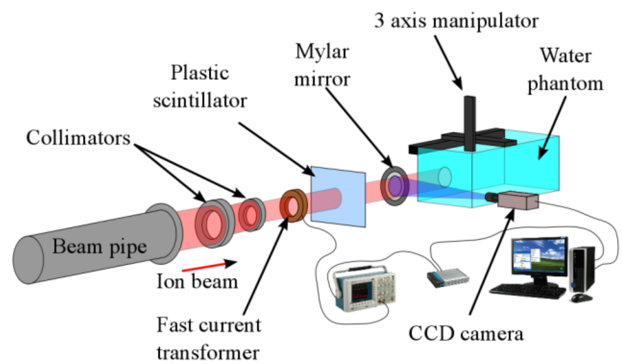

Figure 1: Layout of the experimental setup.

Formation of the dose fields with characteristic transverse dimensions of 20-100 mm was performed by system of magnetic elements, defocusing the ion beam at a considerable distance from the place of exposure and passive collimating system, located in the immediate vicinity of the irradiated target. Homogeneity of the field was controlled by the intensity of the luminescence of the plastic scintillator (Bicron BC412). The image of the beam on the scintillator was transferred to the CCD camera by means of a mirror from metalized Mylar, placed at an angle of 45 degrees to the beam axis.

For measurements of spatial distributions of the absorbed dose to water, as well as alignment of the biological targets during irradiation, was developed and produced water-phantom with the established three-axis manipulator. For readout and analysis of the signals from the detectors and instruments used in the experiment, as well as for operation of the manipulator, developed in ITEP hardware-software complex was used [3].

DOSE-FIELD MEASURMENTS

In the study a beam of carbon ions, accelerated to energy of 215 MeV/amu in the booster synchrotron UK was used. The level of ion accumulation in a storage ring U-10 varied the number of particles per pulse. As in these experiments it was possible to use only ion beam pulses, generated in fast extraction mode, with single pulse width approximately 800 ns (FWHM), firstly questions of the carbon ions dosimetry have been considered. Due to the

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possible height ionization densities in short time period, caused by short width of ion beam pulse and high particle fluence per pulse, additional uncertainties in adsorbed dose determination can occur when widely accepted in clinical dosimetry detectors, such as ionization chambers, are used. To eliminate this problem a method of absorbed dose determination, based on information about particle fluence, measured with fast current transformer, and relative dose distribution in water phantom, measured with point-like silicon detector (SSD), was realized [4]. As an example, Fig. 2 shows the relative depth dose distribution of monoenergetic carbon ion beam in water, measured with the SSD.

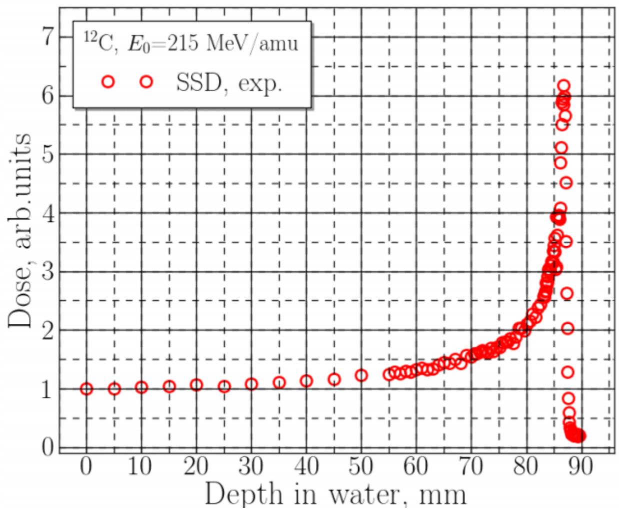

Figure 2: Depth-dose curve.

Although this approach showed reasonable results, with uncertainty not more than 5 %, it is only employed for determination of the ion beam characteristic, e.g. particle fluence, energy and angular distributions, as well as for commissioning of the dose fields required, for biological target irradiation. At the same time for the biological results assurance additional information about dose field homogeneity in target volume is essential. For that purpose radiochromic films were used.

For research was chosen radiochromic film GafChromic MD-V2-55, allowing measurments of the absorbed dose in the range from 1 to 100 Gy. Calibration measurements on a beam of photons with energy of 6 MV, as well as a series of irradiation experiments with carbon ions were carried out. To quantify the observed effect of reducing the sensitivity of the type of films with increasing ions LET, on the basis of the obtained data the dependence of the relative sensitivity of the films as a function of the ion energy was determined. Subsequently, the obtained dependence was used for reconstruction of the iso-dose distributions in the transverse plane to the beam direction based on the measured distribution of the optical density of the exposed film. Dose distribution, measured with GafChromic MD-V2-55 radiochromic film for beam field size with diameter 12 mm at the depth 80 mm in water, is shown in Fig. 3.

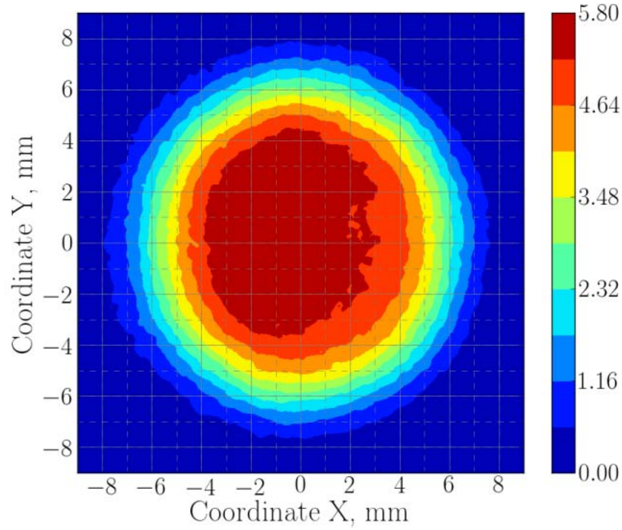

Figure 3: Dose distribution in transverse plane.

RESULTS OF RADIOBIOLOGICAL EXPERIMENTS

"In vitro" Experiments

A series of radiobiological experiments "in vitro" by irradiation with carbon ions of different types of cells, such as tumor and normal. In particular, irradiation was carried out in human peripheral blood lymphocytes (HPBL), mammary cells adecarcinoma Cal51, Chinese hamster cells CHO-K1 and melanoma cells B16F10.

Depending on the size of the target in the preparatory phase prior to the experiments were formed homogeneous dose fields with diameter of 45 mm and 80 mm (inhomogeneity of the field did not exceed 5%). All studies were conducted using a monoenergetic beam of carbon ions with an initial energy of 215 MeV/amu. Irradiation of cells were carried out at two points located at different depths in a water phantom, corresponding to different LET values, with the exception of lymphocytes, irradiated only in the plateau region.

To assess the biological effect of carbon ions in the investigated cell types used two methods. In the case of irradiation of HPBL and Cal51 cell biological efficiency was determined based on the method of analysis of chromosomal aberrations in dividing cells - the so-called metaphase method of analysis of chromosomal aberrations. In the case of irradiation of B16F10 and CHO-K1 cells efficiency of carbon ions was determined by cell survival. As a general method for determining the number of surviving cells a test for colony formation was used. It has to be mentioned, that the results of HPBL irradiation were used as biological method of dosimetry and they were compared with the data of HPBL irradiation with different heavy ions (LET range from 11 to 3160 keV/mkm) in GSI (Darmstadt, Germany) [5]. Table 1 summarizes the results of experiments on the irradiation of the four types of cells held within the reported studies, where RBE is the relative biological

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effectiveness of carbon ions in comparison with x-rays or ^{60}Co photons.

Table 1: Results of the radiobiological experiments

Cell type	Depth in water, mm	LET, keV/mkm	Dose range, Gy	RBE (x-ray)	RBE (^{60}Co)
HPBL	0	16	0-8	1.53	1.77
Cal51	0	16	0-4	-	2.02
	82	40	0-4	-	3.63
B16F10	23	20	0-10	-	1.45
	85	44	0-8	-	2.46
CHO-K1	0	16	0-8	1.65	-
	82	40	0-5	2.27	-

"In vivo" Experiments

In addition to the "in vitro" radiobiological research were conducted several experiments on irradiation of laboratory animals with carbon ions. The study used a laboratory mouse lines C57BL/6 with inoculated melanoma B16F10 tumor.

For the formation of the depth-dose distribution (so-called spread-out Bragg peak), allowing the irradiation of an extended target a comb filters, developed in the Department of Medical Physics in ITEP, were used. Fig. 4 shows the measured with SSD depth-dose distribution for one of the comb filters. The graph shows that the length of the modified peak is about 10 mm, wherein the peak-to-plateau dose ratio corresponds to 1.7.

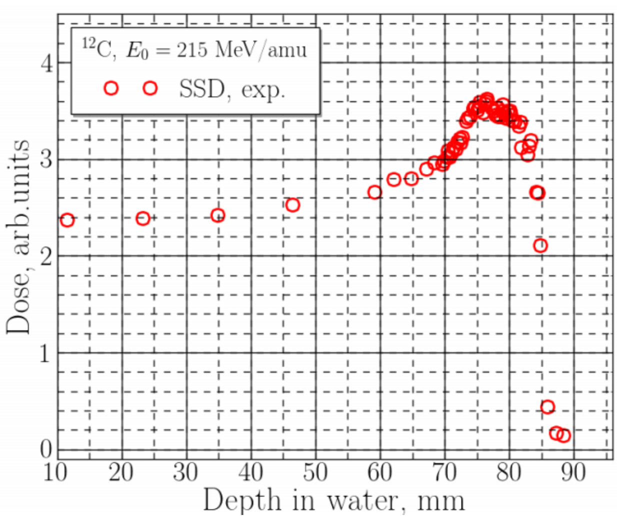

Figure 4: Spread-out Bragg peak.

Based on these results the thickness of the water-equivalent plastic, required for conformal positioning of the spread-out Bragg peak within the tumor location, was calculated. To adjust the position of the tumor relative to the axis of the beam using a system consisting of two semiconductor lasers (Fig. 5).

Further analysis of the results of irradiation showed that for laboratory animals irradiated with carbon ions observed tumor growth delay compared to control animals not exposed to radiation. It was thus demonstrated in principle the possibility of "in vivo" studies on the basis of established in ITEP experimental setup.

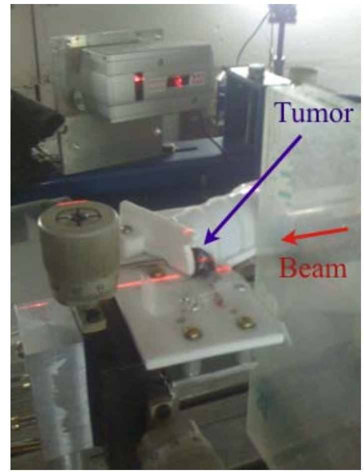

Figure 5: Irradiation of the laboratory animals.

CONCLUSION

An experimental setup for radiobiological research with pulsed heavy ion beams, including corresponding dosimetry system, was created in ITEP. A series of radiobiological research for irradiation of different biological targets were carried out. The further research will be focused on the investigation of various radiobiological aspects of the low-energy protons in the linear accelerator I-2 in ITEP.

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