A high-current nanosecond electron accelerator MIR-M for biomedical research

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Abstract. A high-current electron accelerator MIR-M for biomedical studies of the reaction of healthy and tumor tissues, as well as cell cultures, exposed to X-ray radiation with high dose rate – up to 100 MGy/s at absorbed doses of 0.5 to 20 Gy in the single pulse, was developed and constructed. The main parameters of the accelerator are as follows: accelerating voltage – up to 800 kV, peak current – up to 50 kA, e-beam pulse duration – ≈80 ns. The design and parameters of the main systems of the accelerator together with the methods of measurements and first results of a comparative analysis of the effects of irradiation in vivo and in vitro using therapeutic devices and accelerator MIR-M are presented and discussed.

1. Introduction
The effect of pulsed high-intensity x-rays on cell cultures and tumor tissues with high dose rates, many orders of magnitude higher than the dose rates of therapeutic units, is poorly investigated. To date, the first trial studies have been conducted. One of the first experimental on the study of the impact of ultra-intense photon flux on the biological activity of laboratory animals were performed in 2014 on thermonuclear installation Angara-5-1 at the State Scientific Centre TRINITY together with radiologists from P. Herzen Moscow Oncology Research Institute and Russian Scientific Center of Rentgenoradiology. The results obtained were qualitative in nature and they showed differences in the effect on malignant tumor cells and normal cells of the ultra-intense radiation and the radiation with intensity, typical for the conventional irradiation in the continuous mode. Partially the results are published in paper [1].

To continue the systematic research a specialized experimental stand was constructed at the Joint Institute for High Temperatures of Russian Academy of Sciences. It is based on a high-current nanosecond accelerator MIR-M The accelerator provides studies of the reaction of healthy and tumor tissues to the high-intensity x-ray irradiation with a dose rate up to 100 MGy/s at absorbed doses of 0.5-20 Gy in a single pulse mode.

Below we give a brief description of the main components of the accelerator, methods of dose measurements and results of the first experiments in vivo and in vitro.
2. High-current nanosecond accelerator MIR-M

The Mir-M accelerator includes a modular primary capacitive energy storage, a 20-stage linear pulse transformer, a coaxial pulse forming line (PFL), a step-up transformer with two coaxial transmitting lines (TL) and a high-current electron diode with an anode-converter of radiation. The block diagram of the accelerator is shown in figure 1.

![Figure 1. Block diagram of the accelerator.](image)

The primary energy storage is consists of 10 modules, each of them is a low-inductive assembly of two capacitors of 0.35 µf and one gas switch mounted in one housing. The total energy stored in the capacitors is 5.5 kJ at operating voltage of 40 kV. The description of the module design is given in [2].

Linear pulse transformer includes 20 consequent inductors (ferromagnetic sections) placed inside a metal housing with inner diameter of 275 mm. Each of the inductors consists of a ring ferromagnetic core inside of the primary winding of rectangular cross-section. Ferromagnetic core of the inductors are made of 2NSR alloy with the full scale induction of 3 T in the magnetic field of 800 A/m. The inner diameter of primary winding is 40 mm.

The outer housing and central stalk-voltage adder of 18 mm in diameter with multilayer film-glycerol insulation form the secondary winding. The high-voltage end of the stock is connected to the water insulated PFL through the output conical insulator. The internal volume of the transformer is filled with glycerol.

The design of the linear pulsed transformer and the results of its test are given in paper [3]. The parameters of the simplified equivalent RLC-circuit for the transformer with module capacitive energy storage are as follows: output capacity – 17.5 nF, inductance – 2.2 μH and the total series resistance of 3.2 Ohm.

Nanosecond pulse forming system includes an ordinary coaxial PFL and a step-up transformer with two coaxial lines TL₁ and TL₂ with water insulation, located in a common cylinder with inner diameter of 300 mm. The impedances and electric lengths of the lines are given on the equivalent circuit shown in figure 2.

The PFL charging time is ≈300 ns. The main switch of the PFL (SW₂ in figure 2) is a two electrodes untriggered water switch. A gas switch was used as pre-pulse suppressor SW₃. Now it is
replaced by a water spark gap between two parts of the TL\textsubscript{2} in a zone of an additional crowbar switch installed nearby of the diode insulator.

**Figure 2.** The equivalent circuit of the pulse forming system of the accelerator.

*Electron diode.* The drawing of the basic design of the electron diode for generation of a horizontal photon beam is shown in figure 3. The vacuum volume of the diode is formed by a cylinder with a diameter of 300 mm, a conical high-voltage insulator and a flange with the anode converter unit.

*The insulator* made of Plexiglas serves as an interface between the water-insulated transmission line and the diode vacuum volume. The design of the insulator in the form of a conical diaphragm provides a small inductance ($\leq 100$ nH) of the diode and the ability to withstand pulsed voltage as high as 800 kV. The calculations show that the designed geometry of the insulator and electrodes provides a close to uniform voltage distribution along its vacuum surface. The slope of the electric field lines to the surface lies in the range of optimal angles 30-60°. The cathode holder of increased diameter protects the insulator from the UV-radiation and scattered particles from the accelerating gap.

**Figure 3.** The drawing of the basic design of the electron diode. 1 – high-voltage electrode of TL\textsubscript{2}, 2 – insulator, 3 – cathode holder, 4 – Rogowsky coil, 5 – cathode, 6 – anode (x-ray converter, Ta, 100 $\mu$m), 7 – graphite (Graflex, 0.5 mm), 8 – built-in collimator (Pb), 9 – outlet window (Al, 1 mm)

*The accelerating gap* of the diode is formed by the end part of the cathode and the anode radiation converter foil. Anode flanges with converters of 50 and 90 mm in diameter of Ta foils with a thickness of 100 to 150 $\mu$m were constructed for experiments with photon beams of different transverse sizes. The size of the output beam is defined by a collimator made of Pb that is installed outside or built-in in the anode assembly as it shown in figure 3. The measurements of the space-dose characteristics of photon radiation show that the use of the built-in collimator provides the required radiation gradients and makes it possible to locate the irradiated object close to the outlet window for increasing of the intensity and the total dose.

Figure 4 shows the color pattern (a) and the dose distribution plot (b) for the photon beam at the output of a diode with a built-in collimator with the cylindrical aperture of 20 mm in diameter. Built-in collimators provide a desired dose gradient with the dose decreasing by more than 10 times at the distance of 5 mm in transverse direction from the position of the edge of the collimator channel. Such dose gradients meet the requirements of experiments on irradiation of relatively small tumors of laboratory animals ($\sim 10 \times 10$ mm$^2$).
Figure 4. Colored picture (a) and the cross-section dose distribution plot (b) for the photon beam at the output of the diode with built-in collimator with aperture of 20 mm in diameter.

Comparison of dose of irradiation is complicated by the different methods of dose measurements for two modes with the differences in dose rates of $10^9$-$10^{11}$ times. Film dosimetry is traditionally used on medical installations, and TLD – detectors are used on high-current accelerators. In order to eliminate this uncertainty and improve the reliability of the results we use both methods: TLD-detectors of type DTG-4 with a measuring complex "DOSE-TLD" and a dosimetric film GAFChromic EBT-3. Both types of detectors were calibrated on a medical device "GAMMA" with a Co$^{60}$ radiation source under the same conditions at two dose values – 1 Gy and 7 Gy. The data obtained during the experiments show that at low doses ($\leq$ 5 Gy) the discrepancy between the values recorded by the films and TLD-dose detectors is insignificant. The difference in measurement results is markedly increased at higher doses, up to $\geq$30% at 15–20 Gy. The comparison of the results taking into account the obtained data allows us to make a valid comparison of the biological effects at various dose rates of irradiation.

3. Bio-medical research
Investigation of the influence of high-intensity photon beam on cell cultures was carried out in comparison with the radiation effects of the ROCUS-AM gamma-therapeutic apparatus. The source of radiation "Rokus-AM" is Co$^{60}$. The dose rate of the device was 0.51 Gy/min (8.4 mGy/s). Cells of lines PC3 (culture of cells of a cancer of a prostate, the person), Mel Mtp-x (melanoma) and cells of a line A549 (lung cancer) were used as biological models for research of effects of irradiation in vitro.

For both types of irradiation, cytotoxic effects (early apoptosis, total apoptosis, necrosis) and the effect of irradiation on the level of double-strand DNA breaks were studied.

In the range from 0 to 16 Gy, the study of the level of double strand breaks showed that for the three studied lines, the level of discontinuities depends on the radiation dose. However, there are fundamental differences in the response to radiation for different cell cultures. Thus, for cultures PC-3 (prostate adenocarcinoma) and Mtp-x (melanoma), the level of double-strand breaks induced by high-intensity radiation ("MIR-M") is higher than when exposed these cell cultures to radiation by Rokus-AM. Moreover, as shown in figure 5, for the cells of cultures PC-3 and Mtp-x, the level of double-strand breaks increases significantly when exposed to ultra-high power radiation from 2 to 8 Gy, and when exposed to doses in the range of 14-16 Gy, the differences in the level become minimal. This effect, however, can be explained by the high level of double-strand breaks (more than 60 %) when exposed to doses of 14-16 Gy.

The results of the analysis of apoptosis level (the number of annexin-positive particles) showed that the dependence in this case, have the form of logarithmic curves, the level of apoptosis induced by exposure to high-intensity radiation (MIR-M) is higher than under the influence of gamma-therapeutic installation Rokus-AM. It is also shown that the increase in the level of apoptosis is dependent on the type of cells. For the culture of the Mtp-x at 24 hours of incubation after irradiation, the level of
apoptosis (for MIR-M) lower than after exposure at the Rokus-AM, but after 48 hours of incubation, the level of apoptosis induced by exposure to high-intensity radiation increases rapidly and becomes 2.8 times higher than the level of apoptosis induced by radiation Rokus-AM. When we compare the level of apoptosis in cultures of PC-3 and A549 results differ sharply: in 24 hours after irradiation there are significant differences – level of apoptosis induced by exposure to high-power radiation was significantly higher than after exposure at Rokus-AM. However, after 48 hours of incubation, there were no significant differences in the level of apoptosis after exposure irrespective at MIR-M and Rokus-AM.

Thus, it was shown that the high-intensity radiation of the MIR-M experimental facility has a higher proapoptotic potential. The death of the tumor cell on the way of apoptosis is more preferable during anticancer therapy, since this type of death is not accompanied by damage to surrounding tissues. The predominant induction of apoptosis under the influence of MIR-m radiation is undoubtedly an important factor in assessing the possibility of further use of this type of radiation for medical purposes.

4. Preliminary data on the effect of high-intensity radiation on the growth of experimental tumor model in vivo

Two types of experimental tumors were chosen as a model for the study: Lewis lung carcinoma (LLC), growing on mice of line C57Bl/6 and sarcoma 37, growing on non-native mice. Lewis lung carcinoma is a moderately radiosensitive tumor, an analogue of solid human tumors. Sarcoma 37 is radioresistant. Thus, to identify effects of exposure to radiation of high-intensity was the selected model with different radiosensitivity. Strains tumors were obtained from the collection of the state budgetary institution "Russian oncological scientific center named after N. N. Blokhin" of the Russian Ministry of Health. The tumor inoculation was carried out subcutaneously in the upper thigh of the hind leg. 1 million cells were injected into 0.2 ml of a 199 medium. In each group were 10 mice.

The irradiation was carried out on the 6-th day after tumor inoculation for Lewis carcinoma and on the 7-th for sarcoma 37. Source of conventional radiation was radiotherapeutic apparatus T200 (WOmed, Germany) with an applicator d4/20. The dose rate was 0.65 Gy/min (11 mGy/s). Observation of tumor growth was performed by regular measurements of hip diameter in 2 directions. The multiplication of...
the obtained values was used as an indicator of tumor size. The second indicator of the effectiveness of radiation exposure was life expectancy in the group.

Figure 6 shows the results of observation of the growth of subcutaneously transplanted Lewis lung carcinoma (LLC) in mice of line C57Bl/6. It is shown that mice of the control group, who were not exposed to radiation, are characterized by more intensive growth of the tumor node, on the 12th day after the transfusion the differences between the control and experimental groups are significant.

The given tumor growth curves show the absence of significant differences in the tumor growth rate in the two experimental groups. There are also no differences in survival curves. You can only talk about the trends in the increase of anticancer effect for gamma radiation with ultra high dose rate. However, the different spatial distribution of the dose in the two used equipment allows us to talk about "re-emission" in the case of the T-200 unit, estimated as 15÷20% of the dose received. In addition, the used of irradiation regime was not optimal (50% or more inhibition of tumor growth was not achieved), which suggests the need for a more detailed study of the effects of gamma radiation of ultrahigh power in vivo.

5. Comparative analysis of results of experiments with previously obtained data on irradiation in vivo and in vitro

The obtained results show different levels of relative biological efficiency (RBE) of high-intensity radiation depending on the object under study and evaluation methods. This is consistent with the literature data, which indicate that the data on high-power RBE depend on the studied model [4]. A number of studies have found no significant differences in radiation with a high dose rate in comparison with the usual regime of continuous irradiation [5-7]. Other authors point to a significant increase in RBE determined on the basis of a number of biological indicators, such as the number of emerging DNA double-strand breaks, changes in the parameters of the cell cycle and changes in the level of expression of a number of genes [8, 9]. In a number of studies provided data on the lower RBE for high dose rate radiation [10].

It should be noted that the results of these studies are difficult to compare. They were held in different facilities, in different environments, under differing methods to estimate the effect.

6. Conclusion

High-current electron accelerator MIR-M for biomedical studies of the reaction of healthy and tumor tissues, as well as cell cultures, exposed to X-ray radiation with high dose rate – up to 100 MGy/s at absorbed doses of 0.5 to 20 Gy in the single pulse, was developed and constructed. Experiments on irradiation of cell cultures and laboratory mice with grafted cancerous tumors and a comparative analysis of the mechanisms of cell culture death after irradiation with doses of different capacities was obtained.

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