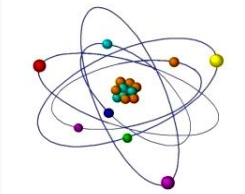
DEVELOPMENT OF BIODOSIMETRY METHODS IN CONNECTION WITH THE IMPROVEMENT OF MEDICAL RADIOLOGICAL EQUIPMENT



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ABSTRACT: *In the last decades the use of ionizing radiation for medical procedures, for treatment and diagnostic purposes, has greatly increased. It is known that in addition to the unconditional benefit, radiation rays can adversely affect healthy tissues which cause radioinducedcomplications. The total effect of the radiation exposure on the whole body and on individual cells depends on the dose of radiation as well as the individual radiosensitivity of the tissues The problem of determining the exact absorbed dose, studying the individual biological reactions of the body under radiation exposure, the search for the most characteristic biological changes for these effects occupies one of the key places in modern radiobiology. Ongoing search for relevant effective biomarkers continues Biological dosimetry is a set of tests that make it possible retrospectively to determine the dose of ionizing radiation absorbed by the body. The analysis of chromosomal aberrations by different techniques is the most developed method of quantifying dose to individuals exposed to ionizing radiations. During the last few decades progress has been made in the field of radiation biodosimetry and numerous biomarkers have been proposed at the level of genes, proteins and other macromolecules. In the field of radiation therapy, everything is changing very quickly. A method of cancer treatment using interactions between radiosensitive drugs and neutrons and proton therapy are introduced. Two major forms of radiation energy are employed in medicine: one is transmission radiation used in both radiology and radiation oncology treatment planning using the external beam, and the other is emission radiation used in nuclear medicine and brachytherapy planning. Some limitations of existing biomarkers in developing methods of radiotherapy are shown. The currently used radiation-dosimetric biomarkers can no longer be universal and a constant search for new effective biomarkers is required. According to the IAEA, extensive international multicenter studies are needed to improve the methodology for the clinical application of biodosimetry. The article provides an overview of the development of biodosimetry methods in connection with the improvement of medical radio equipment*

Key words: cancer, radiotherapy, biodosimetry, markers, individual radiosensitivity

INTRODUCTION

Advances in the treatment of oncological diseases are increasing at an enchanting pace. Despite the annual expansion of the implemented methods, irradiation continues to occupy one of the first places.

When radiation was first used to treat cancer in 1901, it marked a real revolution in medicine. However, this method was developed only with the advent of certain innovative technologies. Today, thanks to advances in physics, technology and computing, radiation therapy methods are becoming significantly more accurate, effective and safe.

X-rays are electromagnetic waves in the range between ultraviolet and gamma radiation. Accordingly, the X-ray machine is a source of ionizing radiation, a serious overdose of which leads to the destruction of the integrity of DNA and RNA chains.

The radiation destroys the DNA structure of cancer cells. Since these cells are defective, the DNA

structure is not restored, as a result of which the cells lose their ability to divide and grow and subsequently die. Healthy cells, which are also exposed to radiation during treatment, have a higher ability to repair because they are not infected: therefore, the likelihood that they will not be damaged during radiation therapy increases [1]. Meanwhile, in all cases, when using X-rays, there is a danger of damage to healthy tissues, which causes radioinduced complications.

There are three methods of exposure: contact (the source of radiation is in contact with human tissues), remote (the source is at some distance from the patient) and radionuclide therapy (the radiopharmaceutical is injected into the patient's blood). Contact radiation therapy is sometimes called brachytherapy.

In addition to radiotherapy, there is also an increasing need to use different doses of radiation for diagnostic purposes. Medical X-ray apparatus as a source of ionizing radiation and high voltage is potentially dangerous. Therefore, a distinctive feature of the operation of X-ray equipment is to ensure the safety of personnel and patients. This is possible with strict compliance with the requirements for the parameters of X-ray technology. The technical serviceability of the equipment and compliance with the norms of its operation is of great importance. More scientific data regarding radiation in medical use and more communication to the medical staff and the public are warranted to optimize the benefit of medical radiation in clinical services [21]. The use of ionizing radiation (IR) medical procedures, for treatment and diagnostic purposes, has recently very increased. Although the general radiobiologic principles underlying external beam and radionuclide therapy are the same, there are significant differences in the biophysical and radiobiological effects. This is raising the problem of management of the results of IR. Results obtained will allow physicians to have a real image of changes in patients' organism caused by irradiation and to make follow up of changes and medically manage them. For persons working with ionizing radiation the basis for developing safety measures is dosimetry. However, physical dosimetry provides only extrapolation information about the dose absorbed by the human organism and does not take into account the individual radiosensitivity of the organism [17]. Different types of radiation may produce different biological effects and the magnitude of the effect can vary according to the rate at which radiation is received (dose rate). The dose rate is a primary factor in determining the biological effects of a given absorbed dose.

The problem of determining the exact absorbed dose, studying the individual biological reactions of the body under radiation exposure, and the search for the most characteristic biological changes for these effects, occupies one of the key places in modern radiobiology. So, in the middle of the last century, a special direction in radiobiology arose –biodosimetry. Biological dosimetry is a set of tests that make it possible retrospectively to determine the dose of ionizing radiation absorbed by the body. The biological dosimetry methods applied in patients undergoing various medical irradiations to low doses.

Post-irradiation damage results are divided into early and late phases. Late irradiation effects appear even after some months or years. Late effects of tissue damage are progressive and irreversible. The total effect of the radiation exposure on the whole body and individual cells depends on the dose of radiation as well as the individual radiosensitivity of the tissues. Because it is a strong mutagen, ionizing radiation primarily causes changes in the genetic structure of living organisms. That's why cytogenetical indexes and parameters are the best markers to detect the biological effects of ionizing radiation [7,8]. Biological dosimetry methods, which are based on the chromosomal damages are very important, because unlike physical dosimetry, it provides the difference between individuals with different sensitivity to radiation. To choose the correct type and doses of radiation are the means not only for optimal results, but also to overcome the radioresistance [1,14].

The analysis of chromosomal aberrations by different techniques is the most developed method of quantifying dose in individuals exposed to ionizing radiations [5,11,13]

In the late 90-s after biodosimetry was started in Georgia and cases of overdose were detected [25], We conducted a survey of medical personnel who had contact with X-ray equipment. These were difficult years after the collapse of the Soviet Union and old, faulty equipment and working conditions in a number of institutions labor was often violated. As a result, the number of dicentric chromosomes in employees exceeded our background data and, in several employees, the received dose exceeded the total dose allowed for professionals (>0,4Gy) The same laboratory conducted a survey of medical staff in a new, well-equipped department, and did not reveal any violations [27]. Since the beginning of this century, both sources of medical exposure and biomarkers that determine the effectiveness and safety of radiotherapy have been constantly improved.

Radiation dosimetric biomarkers have found applications beyond the radiation protection area and now are actively introduced into clinical practice. Cytogenetic assays appeared to be a valuable tool for individualized quantifying radiation effects in patients, with a high capacity for assessing genotoxicity of various medical exposure modalities and providing meaningful radiation dose estimates for prognoses of radiation-related cancer risk [23]. The most common, tested and correct genetic markers of exposure are radiation-specific cytogenetic disorders - stable and unstable aberrations of the chromosomal type.

One of the first additional methods of biodosimetry was the method of determining the level of micronuclei in peripheral blood lymphocytes. [3,6,15] After confirming the informational value of micronuclei, their levels began to be studied in other tissues too [22]. Gradually, other methods of premature chromosome condensation, cytokinesis are being introduced. [10].

The response of different persons to the mutagenic impact varies and depends on individual sensitivity. The data on the proposed biomarkers can be used to predict potential responses to mutagenic factors in specific persons allowing to consider individual sensitivity [26].

The study by us biomarkers (dicentrics, micronuclei, DNA comets) in patients with a tumor of the same localization (laryngeal carcinoma) irradiated with a linear accelerator in 2 gray/fraction mode with a total dose of 70 gy and with “Electra Synergy Platform” apparat, revealed the individual reaction to radiation therapy. Despite one and the same tumor localization and identical received dose of radiation, changes in the studied parameters were not homogeneous. Biomarkers determine not only the absorbed dose but also register the genotoxicity of radiotherapy. It was also demonstrated that the level of micronuclei in buccal cells reliably registers the genotoxic effect of radiation and the individual sensitivity of the patients [12,26].

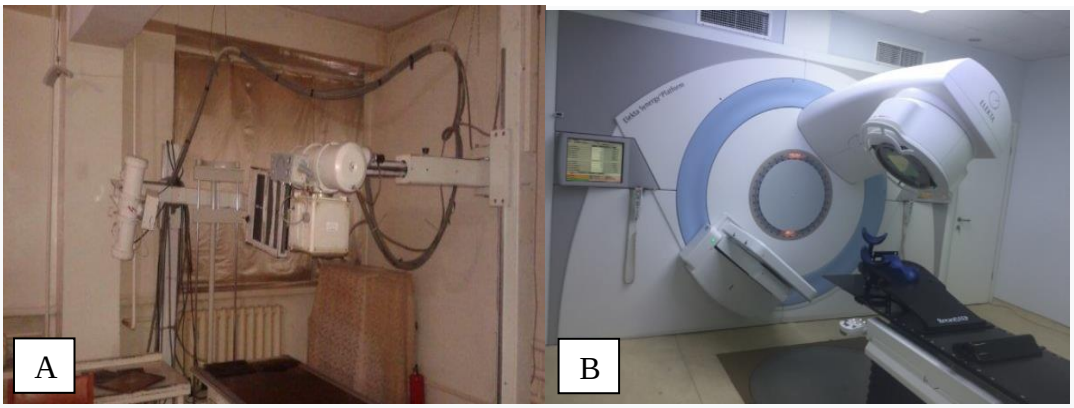


Fig.1 Old (A) and modern (B) X-ray machine

Taking into account that the radiosensitivity of tumors is different even of the same genesis, it is very important to determine the optimal curative regimen for individual patients [24].

During the last few decades, progress has been made in the field of radiation biodosimetry and numerous biomarkers have been proposed at the level of genes, proteins and other macromolecules [16]. Advancements made in radiation biodosimetry at the level of genomics, transcriptomics, metabolomics, proteomics, cytogenetics and electron paramagnetic resonance (EPR) to deal with radiological/nuclear mass casualty incidents have been reviewed [9,18,24].

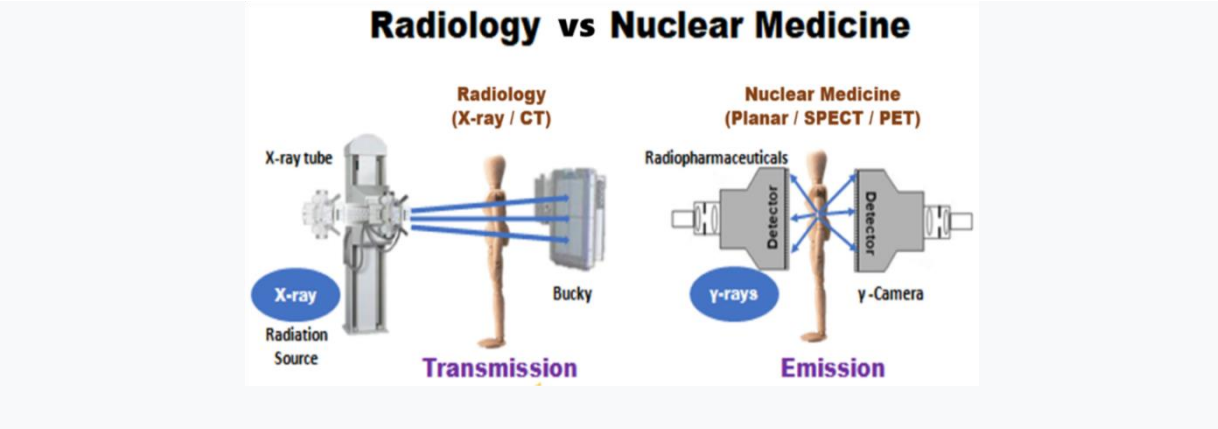
Recent advances in genomic analysis are inextricably linked with the use and development of molecular biology methods: various variants of DNA amplification (RFLP, PCR,) and cytological approaches (chromosome differential staining and in situ hybridization, etc [23] None of the above methods is comprehensive and infallible.

The effectiveness of methods is determined by the degree to which they solve the set tasks, in particular, they characterize directly or indirectly the similarity of DNA between species. Despite all these advances, chromosome analysis remains an important and, for some objects, the main part of genomic analysis. However, for more correct results, it is desirable to use a combination of methods simultaneously [26].

In the field of radiation therapy, everything is changing very quickly. A promising method is proton therapy. The method makes it possible to precisely target a tumor and destroy it at any depth of localization. Proton therapy is attracting attention as a method with high efficiency, characterized by a small impact on the body and a minimum number of side effects. Surrounding tissues receive minimal damage since almost the entire radiation dose is released into the tumor in the last millimeters of the particle path [19].

The perspective effect on healthy tissues with proton therapy compared to traditional radiation therapy allows for the reduction of side effects. If the parameters of irradiation with proton beams are set in accordance with the depth of the pathological focus, at the moment the pathological focus is reached, they are inhibited with the release of the maximum amount of energy without further penetration into the body. The calculation of the optimal irradiation for each patient makes it possible to accurately "remove" the tumor. Along with this, the advantage of the method is to reduce the harmful effects on healthy tissues [20].

Two major forms of radiation energy are employed in medicine: one is transmission radiation used in both radiology and radiation oncology treatment planning using the external beam, and the other is emission radiation used in nuclear medicine and brachytherapy planning. Therefore, radiation protection should be different between transmission and emission radiation.



Different radiation mechanisms of imaging formation between radiology and nuclear medicine departments are shown, for which ways of radiation protection could be different accordingly [3].

A newly emerged medical technology enabling advanced cancer patients to be treated precisely and effectively is diagnostics. With the help of it is possible to kill cancercells while sparing healthy tissue. Internal dosimetry on an individualized basis seems to be clinically needed [3]. So, the existing methods of biodosimetry are still limited in their capabilities.

Different aspects of biodosimetry and scenario-based options for clinical decision support in radiation accidents are presented. New external irradiation biodosimetry deviceDosiKit, based on the dose-dependent relationship between irradiation dose and radiation-induced H2AX protein phosphorylation in hair follicles [2].

According to the IAEA, extensive international multicenter studies are needed to improve the methodology for the clinical application of biodosimetry [23,29].

This was the basis for the launch of the IAEA Coordinated Research Project E35010 MEDBIODOSE: "Application of Biological Dosimetry Methods in Radiation Oncology, Nuclear Medicine, Diagnostic and Interventional Radiology".

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