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Keywords: *brachytherapy, cancer patients, radiation complications, radiobiological support, quality of life.*

DOI: https://doi.org/10.15407/oncology.2025.01.076

PHYSICO-DOSIMETRIC AND RADIOBIOLOGICAL ASPECTS OF MODERN BRACHYTHERAPY OF ONCOGYNAECOLOGICAL PATIENTS

Modern radiation oncology requires individualized prediction of radiation reactions and complications from normal tissues surrounding the irradiated tumor. Currently, contact radiotherapy — brachytherapy using a ^{192}Ir radiation source — is used to treat gynecological cancer in many countries around the world. This uses the volumetric effect on healthy tissues surrounding the tumor, which are exposed to less radiation. This is the so-called "double concern" phenomenon, in which, depending on the physical and dosimetric planning, a small volume of tissue may be exposed to ionizing radiation at a dose that is less or more than planned. Nevertheless, even with the use of modern equipment, there is still a real threat of radiation complications in normal tissues that fall into the zone of therapeutic radiation. For example, during radiation treatment of patients with gynecologic cancer, the pelvic organs are primarily affected. Therefore, the identification of patients at a high risk of radiation complications before the start of radiation therapy remains the challenging problem of modern oncology. Based on the literature data and our own research, the way to determine radiobiological indicators that takes into account the mechanisms of radiation damage formation and predictors of the increased risk of complications of radiation therapy in cancer patients is outlined. The article focuses on the analysis of the quality of life of treated patients. The information on the quality of life is obtained based on the questionnaires filled by the patients themselves as well as the objective analysis of the clinical parameters. Summarizing the material presented in this article, it should be emphasized that brachytherapy is recognized as a modern high-tech and effective method of radiotherapy for gynaecological cancer. Radiobiological support of brachytherapy allows predicting the risk of developing radiation complications, which increases its effectiveness and the quality of life of treated patients.

In recent years, there has been a rapid increase in the incidence of gynaecologic malignancies. Currently, brachytherapy (BT), i.e. contact radiation therapy, is widely used in many countries of the world for the treatment of patients with endometrial and cervical cancer [1–5]. In addition to BT, the treatment protocol includes remote therapy, and the combination of these two methods in the world is the "gold standard" for treatment of tumours of female reproductive system. The use of the latest technologies in radiation oncology makes it possible to form dose fields more rigidly with the minimal capture of normal tissues at an optimal radiation load on the tumour. The main reason for prescribing BT is the way in which ionizing radiation (IR) dose is delivered and distributed. This takes advantage of the volumetric effect on healthy tissues surrounding the tumour, which receive a lower radiation load. This is the so-called "double concern" phenomenon, whereby, depending on the physical-dosimetric planning method, a small volume of tissue may be exposed to a higher or lower dose than the planned IR dose.

The irregularity of the irradiation field around the implanted IR source causes certain radiobiological differences. The dose rate near the irradiation source is high. As the cells move away from the source of IR, they show less radiosensitivity and the dose rate decreases.

Currently in radiation oncology, BT in pulse mode is used for treatment of gynaecological cancers. High dose rate in the pulse diminishes radiation-induced damage repair processes. Tissues that are slowly repaired are affected to a greater extent. As a result, the difference in the therapeutic index between rapidly repairing tumour and slowly repairing cells of healthy surrounding tissue changes.

When using modern radiotherapy equipment, there remains a real threat of radiation complications in healthy organs and tissues that fall within the irradiation zone. For example, when treating patients with

gynaecological cancer, critical pelvic organs suffer. As a consequence, cystitis, rectitis, and enterocolitis may develop. Cells of the circulating blood pool, especially highly radiosensitive T-lymphocytes, are also damaged. Concomitant chronic diseases, such as diabetes mellitus, thyrotoxicosis, etc., may be factors in increasing the radiation response of the organism of patients. A number of researchers connect the radiation complications with prescription in some cases of high single and total doses of IR, which exceed tolerance of tissues surrounding the irradiated tumour [6]. Therefore, the problem of radiation oncology and clinical radiobiology is the identification of patients at a high risk of radiation complications before the start of therapy.

As a consequence of RT, 14–80% of oncogynaecological patients may experience adverse radiation reactions of different intensity. They are forced to interrupt the treatment that undoubtedly affects its results, as well as worsen the quality of life (QOL) of treated patients [6]. Therefore, the solution of the problem of damage to normal (non-malignant) cells, which fall into the zone of therapeutic irradiation, remains relevant for increasing the efficiency of modern radiation treatment.

Knowledge of physical and dosimetric characteristics of the main sources of IR used in modern BT and radiobiological paradigms make it possible not only to predict the probability of tumour resorption after IR exposure, but also the risk of late radiation complications.

PHYSICO-DOSIMETRIC ASPECTS OF BRACHYTHERAPY

It is known that brachytherapy should form, reproduce, and ensure the high accuracy of dose distributions in a course of malignant neoplasm irradiation along with providing the safety of medical personnel [1]. Ability to deliver the maximal doses of radiation directly to the tumor with minimal exposure of, critical and related organs is an important advantage of intracavitary radiation therapy. The secondary vaginal cancer treatment protocol in addition to BT includes the external-beam radiotherapy (syn. teleradiotherapy). Combination of these two methods is a "gold standard" for the treatment of tumors of the female reproductive system worldwide. Over the last decade, it has emerged as a high-tech, effective, organ-preserving, and state-of-the-art component of radical radiation treatment of gynecological cancer, enabling a significant reduction of radiation exposure to the critical and inter facing organs [7, 8]. To provide effective brachytherapy, the gamma-radiation source is to meet some specific requirements, namely the radiation energy in the range of 0.2–0.5 MeV, high specific activity, small size, and half-life corresponding to the acceptable frequency of recharging [1].

Application of the iridium-192 (^{192}Ir) radioisotope sources with an activity of 5–10 Ci is feasible in the modern brachytherapy installations with a high dose rate of ionizing radiation [9]. Such sources are becoming increasingly popular despite relatively short half-life of the isotope (73.83 days). The latter accordingly necessitates frequently recharging of the device i.e. about 3–4 times a year. There are some key advantages of the ^{192}Ir, namely a relatively low average energy of its gamma-radiation (0.38 MeV), thus the mass of storage can be dramatically reduced, and most importantly from a clinical point of view that a variety of shadow screens for effective local protection of vital organs and tissues can be applied. Moreover, the higher specific activity of ^{192}Ir (450 Ci/g) allows the use of smaller size sources while providing the irradiation at a high dose rate (>12 Gy/h). A small diameter of the ^{192}Ir source (1.1 mm) is of especial importance as allows creating thin applicators with 3 mm in diameter, the installation of which often require no anesthesia. The facts that the ^{192}Ir half-life is 22-fold shorter compared to ^{60}Co and it can be administered in a fractionated mode of RT are also meaningful.

Development of modern automated systems for the delivery/placement of ionizing radiation sources controlled by a computer allows performing brachytherapy in a pulsed mode. Presence of intervals between pulses gives a slightly greater degree of freedom to the patient and more radiation safety to the medical staff. Therewith, this mode of therapeutic exposure allows making a correction for the decay of radioactive isotope, which in turn minimizes side effects that can adversely affect the quality of treatment. The issues regarding recommendations of the safe RT when using a pulsed mode continue to be discussed by the experts [4]. It should be noted that any deviation from the mode of continuous irradiation towards the interval mode might be accompanied by the radiobiological adverse effects. This is because the dose rate becomes higher with each pulse and leaves less chance to radiation-induced DNA damage repair, among others in healthy tissue cells surrounding the tumor. When using the automated delivery systems of ionizing radiation source with a high dose rate, a potential increase in tumor radioresistance can occur due to inadequate reoxygenation of tumour cells, which should be taken into account when planning the RT.

Thus, the use in modern radiation oncology of new BT technologies with high dose rate sources ^{192}Ir allows achieving maximum distribution of absorbed dose in the tumour focus of gynaecological patients and minimum radiation load on critical tissues and organs from its surroundings.

RADIOBIOLOGICAL ASPECTS OF BRACHYTHERAPY

Based on the literature data and results of our own studies, we outlined the way of determining among the main radiobiological indicators, which take into account the mechanisms and stages of radiation damage

formation, the predictors of complications due to RT in patients with oncogynaecologic malignancies. They include, first of all, cytogenetic indicators (chromosome aberrations), which form genome instability. This will allow singling out the group of increased risk of the development of the negative BT effects, to exploit an effective way of pathogenetic therapy preventing the damage of healthy surrounding tissues and thus to reduce the frequency, nature, and severity of the distant adverse complications of RT in this category of patients. Such an algorithm of radiobiological support of BT will contribute to the improvement of QOL of treated patients [10]. It is especially important to consider it when combined (remote and contact) radiotherapy is prescribed.

Performing the radiobiological dosimetry based on a test system of peripheral blood lymphocytes (PBL) in gynecological cancer patients followed by the cytogenetic analysis of radiation-induced chromosome aberrations is one of the fruitful approaches to increase the ^{192}Ir BT effectiveness [11]. The high mobility of lymphocytes in the bloodstream, the distribution of lymph nodes throughout the body, and the ability of these cells to accumulate chromosome aberrations make it possible to assess the radiosensitivity of the patients" organism as a whole. The test-system based on PBL and their cytogenetic analysis is designated as the "gold standard" for bioindication of human irradiation. The author"s long-term experience, including the development and implementation of relevant methodological recommendations, for example, [12] prove that the compliance with the appropriate standards of PBL cultivation, metaphase analysis of chromosome rearrangements will exclude subjective judgement on the results and increase the correctness of their evaluation when examining cancer patients.

We have previously found [3] that in primary/naive patients, the total incidence of chromosome aberrations before the course of ^{192}Ir-brachytherapy was 6.6 per 100 metaphases (from 3.6 to 8.8 aberrations per 100 metaphases), which was twice the value of the healthy control. After the first fraction of local irradiation, the total incidence of chromosome aberrations was 29.0 per 100 metaphases (from 18.0 to 37.0 aberrations per 100 metaphases). Radiation markers, namely the dicentric chromosomes with an accompanying paired fragment dominated in the spectrum of radiation-induced damage. The variability of individual values of cytogenetic parameters of PBL after the first TR fraction in the same dose (5 Gy) indicates the individual sensitivity of patients to the ^{192}Ir gamma-irradiation.

The predominance of chromatid-type aberrations in the spectrum of PBL lesions (66%) indicates the formation of genetic instability, as well as low efficiency of repair processes. In addition, the chromosomal instability in adjacent healthy cells may be associated with humoral factors that circulate freely in the blood — "bystander-effect". The radiobiological data we have obtained unambiguously indicate that blood T-lymphocytes (a model of highly radiosensitive human cells) are "compromised" even before RT due to their genetic status. The researchers believe that molecular, chromosomal, and other abnormalities in healthy cells of primary cancer patients alter the functional status of these cells, including radiosensitivity, and therefore give reason to consider them only conditionally normal. Additional radiation-induced damage in these cells due to therapeutic irradiation may cause a high risk of developing distant radiation complications from healthy tissues surrounding the tumour [13, 14].

Radiobiological support of RT in oncogynaecological patients indicates the expediency of a personalized approach to planning the course of therapeutic irradiation, which will increase the effectiveness of treatment and quality of life.

QUALITY OF LIFE CRITERIA FOR CANCER PATIENTS: CURRENT TREND

The analysis of patients' quality of life (QOL) is a promising and relevant area that allows improving the provision of medical care and the outcomes of their treatment [15]. Cancer patients are the main category of patients for whom quality of life is assessed in clinical trials. The leaders among the countries performing such studies are recognised to be the countries of Europe (Germany, Spain, etc.), the USA, Asia (South Korea, China). In 1990, the American Society of Oncologists declared the QOL to be the second most important criterion of patient treatment efficiency after the overall survival rate.

Currently, a comprehensive approach to improve the QOL of cancer patients after completion of therapy includes social and psychological support, as well as the prevention of complications arising after treatment, and monitoring of health status over a long period of time. With regard to oncogynaecological patients, QOL is closely related to the prognosis and treatment of late complications of therapeutic irradiation.

It has been established that the indices of QOL of cancer patients correlate with the complications of the combined (radiation + chemotherapy) treatment and justify the need of their correction.

The QOL is assessed by the standardised questionnaires filled in by the patients themselves. In this case, questionnaires are used to assess symptoms, such as depression, weakness, nausea, and others. Changes in the parameters of oncological patients' QOL are largely determined by the stage of tumour process development, the effectiveness of treatment and rehabilitation. By improving the results of cancer therapy, it is possible to keep the QOL at a satisfactory level for a long time.

The analysis of the literature data and accumulated world experience in the new direction of oncology allow

us to conclude: the main principle of the assessment of QOL is that qualitative and quantitative information about the state of a cancer patient and his problems can be obtained only with the help of the patient himself. The data on QOL should be analysed in combination with clinical parameters. This will objectify the assessment of QOL and bring closer to the personalisation of treatment and prognosis of its efficacy.

CONCLUSION

Summarizing the material presented in this article, it should be noted that BT is a modern, high-tech and effective method of radiation treatment of gynaecological cancer. The use of BT allows increasing the efficiency of RT and minimising the radiation load on normal organs and tissues surrounding the tumour. The radiobiological support of BT using a high-power ^{192}Ir IR source will allow predicting the risk of radiation complications, especially in combination with remote irradiation of the tumour focus.

The work was carried out under the topic No. 2.23. 5.418 "Determination of predictors of radiosensitivity of peripheral blood lymphocytes of patients with endometrial cancer in vitro and under the action of a protector *ex vivo*.

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ФІЗИКО-ДОЗИМЕТРИЧНІ ТА РАДІОБІОЛОГІЧНІ АСПЕКТИ СУЧАСНОЇ БРАХІТЕРАПІЇ ОНКОГІНЕКОЛОГІЧНИХ ХВОРИХ

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РЕЗЮМЕ. *Сучасна радіаційна онкологія потребує індивідуального прогнозування променевих реакцій та ускладнень з боку нормальних тканин, що оточують опромінювану пухлину. На даний час для лікування гінекологічного раку у багатьох країнах світу використовується контактна променева терапія — брахітерапія з використанням джерела опромінення ^{192}Ir. При цьому використовуються об'ємний ефект на здорові тканини із оточення пухлини, які зазнають менше променеве навантаження. Це так званий феномен "подвійного занепокоєння", при якому в залежності від фізико-дозиметричного планування, невеликий об'єм тканини може зазнавати дії іонізуючої радіації в дозі, яка менше або більше запланованої. Тим не менше, навіть при використанні сучасної апаратури, залишається реальна загроза розвитку променевих ускладнень в нормаль-*

них тканинах, які попадають в зону терапевтичного опромінення. Наприклад, при променевому лікуванні онкогінекологічних хворих "страждають" перш за все органи малого тазу. Тому проблемою сучасної онкології залишається виявлення хворих з високим ризиком виникнення променевих ускладнень ще до початку протипухлинної терапії. На підставі даних літератури і власних досліджень окреслено шлях до визначення радіобіологічних показників, які враховують механізми формування променевих пошкоджень та предикторів підвищеного ризику ускладнень променевої терапії онкологічних хворих. В роботі приділяється увага аналізу якості життя пролікованих хворих. Саме така інформація має бути отримана тільки за допомогою самого пролікованого хворого у поєднанні з клінічними параметрами. Узагальнюючи представлений у статті матеріал, слід підкреслити, що брахітерапія визнана як сучасний високотехнологічний та ефективний метод променевої терапії гінекологічного раку. Радіобіологічний супровід брахітерапії дозволяє прогнозувати ризик розвитку променевих ускладнень, що підвищує її ефективність та якість життя пролікованих хворих.

Ключові слова: брахітерапія, онкологічні хворі, променеві ускладнення, радіобіологічний супровід, якість життя.

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Одержано: 27.03.2025