INTRODUCTION

According to the review of the UK Royal College of Radiologists, successful treatment of cancer patients is currently achieved by surgical operations (49%), while contribution of radiation therapy (RT) and chemotherapy (CT) is about 40 and 11%, respectively [1]. However, certain evidence now exists that despite of all technical improvements, RT (as monotherapy or in combination with other types of treatments) is effective in 52% of cancer patients [2]. One of possible reasons for such low effectiveness of RT may consist in prescription of this type of therapy without pilot evaluation of tumor cell radiosensitivity in the patients, changes in DNA repair systems, and some other related processes during and after radiation treatment. Analysis of sensitivity to some chemotherapeutic agents is already used in targeted CT of cancer patients (e.g., in the case of prescription of trastuzumab and tamoxifen) [3], but is still not used in RT as clinical practice does not have reliable predictive markers of biotesting.

Based on analysis of predictive markers it is possible to select groups of patients for prescription of certain therapeutic schemes. In contrast to prognostic factors, which usually represent parameters of developmental biology of the tumor process, predictive markers provide some information on possible benefit of planned therapeutic treatments in certain patients. This is one of basic principles of personalized therapy. Determination of such biomarkers frequently includes analysis of tumor tissue or blood samples for detection of sensitivity or resistance to the planned therapeutic scheme. The final goal of such biotesting consists in identification of a parameter, which would help to select certain scheme for treatment of the patient. At the same time, methods of marker determination have to be reasonably rapid for monitoring of therapeutic treatment as metabolic changes in the patient body may result in a decrease and even loss of effectiveness of the initially planned therapeutic scheme. Although search for such biomarkers has already started, interdisciplinary clinical studies (including analysis at the molecular level, see below) have not yet come to unambiguous conclusions. Prediction of the therapeutic effectiveness, taking into consideration radiosensitivity, may not only select patients responding to the protocol scheme of RT, but also identify patients, who do not respond to such therapy and therefore should avoid it for selection of other schemes of therapy.

In 2002, the problem of predictive testing of radiosensitivity in cancer patients was presented by the International Atomic Energy Agency (IAEA) as a project for coordination study in this field [4]. In 2005, when molecular testing capacities could not be ignored, IAEA organized a meeting in Amsterdam in order to give the international dimension to this problem. The report of this meeting indicated only a few of types of such studies, as also the development of new initiatives that were running in the world using the
bank of tumor and non-tumor tissues samples that would represent a basis for the development of molecular markers, predicting patient’s response to RT [5]. These studies were based on early known clinical tests (e.g. [6]) and also tests based on mathematical treatment of cytologic analyses demonstrating that the overall positive outcome of treatment for the population of patients could be theoretically achieved if the radiation doses changed according to available information on cellular radiosensitivity of patients [7].

However, by the end of XX—beginning of XXI century, it became clear, that tests based on cell analysis still had low sensitivity and specificity. For example, being an informative predictor for evaluation of effectiveness of combined and adjuvant CT in patients with breast cancer or Hodgkin’s lymphoma, myelosuppression was an insignificant parameter for organ-sparing treatment of patients with bladder cancer [8–12]. In addition, results of testing could be obtained only after the beginning of the therapy. In the future, molecular tests with a wider range of applications appear to be more reliable, and susceptible to better standardization [5, 6, 13, 14]. Soon after that a project for the development of genetic predictors of adverse radiotherapy effects (GENE-PARE) was issued [15]. It was suggested that realization of this project would give useful information for optimization of personified treatment taking into consideration genetic data as individual characteristics of the patient. In 2008, in New York a meeting “Prediction of individual radiosensitivity: technology of the present and the future” was organized at the Columbia University [16]. Since radiologists already accumulated results of numerous observations, one of the objectives of this meeting was to discuss the importance of individual radiosensitivity for development of predictive parameters of early and late effects of radiation, induced by RT. Thus, identification of molecular markers predicting therapy response of a certain patient becomes the key point in this field.

In Russia prescription of radiotherapy to cancer patients is still based on a complex of clinical data on the nature of the tumor, prognosis of its distribution, the state of the patient, age, comorbidities, as well as on the intuition of the physician, depending on his personal experience. Such indirect parameters as radiosensitivity of the tissue, from which the tumor originates, tumor growth index, and also hematological (hemoglobin, number of leukocytes, group statistical data) and some other parameters are also taken into consideration. In addition it should be noted that tumors of the same histopathological type are very heterogeneous in responses of their biochemical processes to radiation. Reactions of tumor and non-tumor tissues on radiation treatment are very individual in individual patients and this influences the overall therapeutic effect of ionizing radiation in each patient. In this context it is important to develop reliable biological markers, which would predict reaction of tumor(s) and body of each patient to planned RT schemes and thus to individualize the therapeutic treatment. However, at the present time in Russia determination of tumor cell radiosensitivity in patients receiving RT is rather episodic. Lack of proper evaluation of radiosensitivity explains lower values of RT effectiveness in the treated patients (20–40%) [13], as compared with the above cited report (32%) [2]. However, in order to increase radiosensitivity of tumors various methods of radiomodification and polyradiomodification have been proposed. [17].

The aim of this review is not only to make a comprehensive analysis of the results obtained in this direction (most of which have not yet reached the major goal), but also to substantiate new ways for an adequate solution of the problem.

1. MATERIALS AND METHODS OF ANALYSIS

1.1. Material for the Studies

Results of numerous studies on quantitative analysis of radiosensitivity tested for prediction of RT results may be summarized as follows. Some of these tests were performed to predict tissue sensitivity of tumors, while the other tests were carried out to predict injury of non-tumor tissues (including blood cells). Using methods of fibroblast cultivation it was demonstrated that results of in vitro testing correlated to early (but not late) reactions observed in clinical practice [18]. The use of tumor cell microcultivation appears to a more appropriate approach for determination of tumor cell sensitivity to various therapeutic treatments [19]. However, it should be noted that parameters of tumor cells radiosensitivity are not always reliable predictors of the effectiveness of radiation therapy [20]. At the same time, when tissues surrounding tumors were histologically determined as more or less normal, occurring biochemical abnormalities suggested that they were not normal. These abnormalities included impaired methylation [21, 22], telomere shortening [23], altered response to estradiol [24], loss of retinoic acid beta receptor expression [25], etc.

Analysis of global gene expression revealed transcription differences in epithelium of healthy patients (EHP) and histologically normal appearing epithelium of terminal ductal lobular units of breast cancer patients (epithelium of cancer patients (ECP), at the distance of 1–2 cm from the tumor) [26]. Authors found transcription differences in EHP and in CIS (carcinoma in situ) and the ECP transcription pattern was in 82% closer to that of CIS than to EHP. In ECP gene transcription was less active than in EHP. The authors concluded [26] that in ECP histologically recognized as normal at the early stages of carcinogenesis, there was abnormal (similar to malignant) global gene expression and, consequently, metabolic impairments. These abnormalities could serve as markers of latent