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Original research article

Radiobiological models in prediction of radiation cardiotoxicity☆

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ABSTRACT

Coronary disease induced by previous radiotherapy is the most common cause of death among patients treated with radiotherapy for cancer. Risk factors that may affect the frequency and intensity of radiotherapy's cardiac toxicity are primarily the radiation dose and the volume of the heart exposed to radiation. The prolonged survival time of patients after radiotherapy, but also the intensive development of modern radiotherapy techniques results in the necessity of precise estimation of both tumor control probability, and the risk of normal tissue damage, thus the models describing the probability of complications in normal tissues have also been developed. The response from the cardiovascular system to high-dose radiation is known and associated with a pro-inflammatory response. However, the effect of low doses may be completely different because it induces an anti-inflammatory response. Also, there is no unambiguous answer to the question of whether RICD is a deterministic effect. Moreover, there is a lack of literature data on the use of known radiobiological models to assess the risk of cardiovascular complications. The models described are general and concerns any healthy tissue. Therefore, when planning treatment for patients, particular attention should be paid to the dose and area of the heart to be irradiated.

1. Introduction

Coronary disease induced by previous radiotherapy is the most common cause of death among patients treated with radiotherapy for cancer.[1] The final products of water radiolysis are reactive oxygen species that cause oxidative stress, DNA damage, and lipid peroxidation. As a result of lipid peroxidation, lipid peroxides and toxic aldehydes appear in cells,[1,2] which may cause damage to cells (including endothelium), capillaries and coronary artery spasm.[3] For many years, the heart was considered to be a resistive organ.[4] However, many epidemiological data point to the relationship between exposure, even to small doses of radiation and subsequent heart failure.[5–7]

The main symptoms of radiation-induced cardiotoxicity, especially in the case of historical irradiation techniques, are acute pericarditis and pericardial effusion. There may also be arrhythmias, heart valve diseases, conduction defects, cardiac fibrosis and cardiomyopathy (as a result of myocyte ischemia), acceleration of atherosclerotic processes (as a result of endothelium damage and reduced availability of nitric oxide) and sporadic secondary heart cancer.[8–11]

Risk factors that may affect the frequency and intensity of radiotherapy's cardiac toxicity are primarily the radiation dose and the volume of the heart exposed to radiation (the risk of complications increases dramatically after exceeding 50 % of the irradiated heart volume). The irradiation technique, prior chemotherapy, age of the patient (risk increased in patients under 20 years of age) and the time that has elapsed since the end of therapy (the risk increases over time),[8,9,11,12] are also important. Risk factors also include diabetes, obesity, hypertension, and smoking.[9,11,12] In the past, the use of simple radiotherapy techniques (e.g., the method of alternating fields) was associated with an increased risk of cardiovascular complications in patients treated for left breast cancer (compared to patients treated for right breast cancer).,[10,12] Beginning in the 1970s and 1980s, due to the development of conformal irradiation techniques, the risk of cardiac death after radiotherapy of breast cancer began to diminish.[13–15] Old radiotherapy techniques were associated with frequent radiation changes in the pericardium. Acute pericarditis occurred in 20–40 % of patients at doses above 40 Gy for more than 50 % of the heart volume.[16] Currently, the most common late complication of radiotherapy is coronary artery disease, manifesting after 10–15 years following the end of treatment.[9,11] Long-term observation of patients (10–15 years) also indicates a frequent heart disorder, occurring in 29 % of patients. The myocardium itself, due to its low mitotic activity, is relatively resistant. However, in 4 % of patients after a dose of 35 Gy radiation, disturbances of the LVEF parameter are observed, and a late radiation-induced reaction may also occur, which is

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associated with cardiac fibrosis and cardiomyopathy.[17] Cardiotoxic effects may increase the use of anthracyclines, immunotherapy, and systemic therapy.[18] The combination of modern techniques of conformal radiotherapy with antibiotic treatment increases the risk of heart failure by approximately 5 % of patients.[19]

2. Cardiotoxicity

The National Cancer Institute (NCI) experts define the cardiotoxicity of anticancer treatment as a complication that affects the heart.[20] The European Society for Medical Oncology (ESMO) extend this definition to include other cardiovascular complications that may occur during anticancer treatment: left ventricular dysfunction, heart failure, myocardial infarction, arrhythmias or conduction, acute myocarditis or pericarditis, hypertension arterial or hypotonia, and in the case of radiotherapy – coronary heart disease.[21] According to the American Society of Echocardiography and the European Association of Cardiovascular Imaging, the oncological cardiotoxicity is diagnosed, when the left ventricular ejection fraction (LVEF) is reduced by more than ten percentage points to below 5 %, i.e., below the reference value in 2D echocardiography.[22] Based on the time of occurrence and the type of clinical symptoms, four types of cardiotoxicity can be distinguished related to oncological treatment: acute, subacute, early chronic, and late chronic.[23] The main risk factors for cardiotoxicity of radiotherapy are young age at the time of exposure, accompanying diseases (diabetes, obesity, hypertension, dyslipidemia), high total dose (above 30–35 Gy), fractional dose above 2 Gy, hormonal treatment. Cardiological complications of radiotherapy are most often distant in time and recognized even ten years after irradiation, especially in patients treated in their youth, but may also occur in the form of acute toxicity. The acute phase mediators are tumor necrosis factor (TNF) and interleukin (IL): IL-1, IL-6, IL-8, whose activity leads to neutrophil infiltration. Acute toxicity may occur asymptomatically or in the form of acute pericarditis. Chronic toxicity is associated with fibrosis induced by inflammatory factors, such as IL-4, IL-13, and transforming growth factor ß (TGF-ß). In the pathohistological picture of counseling changes in the heart, inflammatory cells, fibroblasts, and collagen are observed. Myocardial fibrosis then leads to a reduction of LVEF and heart failure. In the vascular mechanism, atherosclerosis, endothelial fibrosis, minor vascular lesions, and conduction abnormalities are observed.[24] Radiation-induced cardiotoxicity occurs most often in the form of coronary artery disease, valves, myocardium and cardiac conduction system, and functional disorders diastolic,[21] but cases of myocardial fibrosis are also known.[25]

3. Epidemiology

The epidemiology of radiotherapy-induced cardiovascular disease (RICVD) is complex, which results mainly from the constant development of dosimetry methods and the use of protective covers to reduce the negative impact on the heart. Another factor hindering the assessment of the scale of the phenomenon is the specificity of the appearance of late effects (often after many years), such as damage to the circulatory system. There are four pathological changes induced by radiotherapy in the cardiovascular system: pericarditis (both acute and chronic), cardiomyopathy, valvular heart disease, and coronary heart disease.[1]

Early pericarditis is currently rarely diagnosed due to dose reduction on the heart due to advanced dosimetry. The clinical symptoms may occur during radiotherapy with a tolerance dose of 36–40 Gy or above 50 Gy in a volume above 30 %.[26] The most common complication after radiotherapy is chronic pericarditis. This side effect is highly dose-dependent: it increases by 40 % with a dose increase from 50 to 60 Gy. The number of chronic pericarditis cases decreased significantly with the advent of modern radiotherapy techniques reducing the risk of cardiac irradiation.

Nevertheless, studies by Duane et al., and McGale et al. indicate an increase in the risk of chronic pericarditis in patients after left breast radiotherapy 1.6 times compared to the group treated for right cancer.[27,28] The latest epidemiological data indicate that radiation-induced cardiomyopathy, RICM, occurs, on average, after 40 years following the end of treatment in nearly 25 % of patients, although the majority of these cases are induced by heart damage (valvular disease or myocardial infarction). Statistically, the risk of symptoms increases after five years from the end of therapy but may evolve many years later.[29]

RICM is characterized by a spreading inflammation accompanied by perfusion disorders, progressive fibrosis, and damage to the peri-myocyte endothelium. A number of these changes, especially flow disturbances, can be detected in PET. The incidence of valvular heart disease (VHD) varies depending on the dose used. Therefore, it is related to the years in which the patient underwent radiotherapy. Aleman et al. indicate that the risk of VHD was seven times higher in patients treated in the 1960s than at the end of the century.[30] The most frequently observed change is a regurgitation of the mitral valve and aortic valve, while stenosis is most often associated with the aortic valve. Radiation-induced coronary heart disease (CHD) is currently the subject of intense research, although it was considered controversial until the 1990s. Increasing survival time and extended epidemiological studies have allowed a more accurate study of CHD, and may even be triggered by a dose of about 10 % less than the dose of cardiac tolerance and more often than other forms of RICVD. The risk of CHD increases with follow-up time and reaches statistical significance after 20 years from the end of therapy.[31]

4. Radiobiology modeling of cardiotoxicity

The prolonged survival time of patients after radiotherapy, but also the intensive development of modern radiotherapy techniques results in the necessity of precise estimation of not only tumor control probability, but also the risk of normal tissue damage. For several decades the total dose in radiation therapy has been determined empirically. The curves representing tumor control probability (TCP) dependence on the total dose have been determined based on retrospective studies to determine the lethal dose (LD) or dose causing local curability of the tumor (or other effects) in 50 % of cases. Those curves have a sigmoid shape, where radiation effect is close to zero when the dose is close to 0, and the radiation effect is close to 100 % at large doses.

Several mathematical models were developed to describe the effect of radiation (P) in the function of dose (D). The most known are the logistic, the probit, and the Poisson dose-response models.[32] The probit and logistic models are more simple to apply to the mathematical description of extensive clinical data but have no biological justification. Thus, they are less useful, although they have a sigmoidal shape. Both dose-response models are widely used in biological study, beside radiobiology.

The publication by Munro and Gliberts in 1961 of the target theory and the nature of cell killing by ionizing radiation has contributed to the development of the model currently used in radiobiology studies. Briefly, this formula determined the probability of curing a certain number of tumors, each of them consisting of N number of identical cells.[33] With the increase in radiation dose, the clonogenic survival of cancer cells decreases, therefore tumor cure probability increases. This increase is not linear and depends on the death of the last surviving clonogenic cell. Considering the random nature of cell death after irradiation of identical tumors

with the same radiation dose, we will obtain a randomly distributed (Poisson) number of clonogenic cells surviving on the tumor.

This dependence can be expressed by the equation:

$$TCP = e^{-\lambda}, \quad (1)$$

where TCP is tumor control probability, and λ means the average number of clonogenic cells in the tumor. The assumption of Munro and Gilbert that λ is a negative function of dose and allows obtaining a typical sigmoid shape dose-response curve, which was later replaced by the linear-quadratic model.

Accordingly to TCP, a model describing the probability of complications in normal tissues was also developed. The curves illustrating the normal tissues complications probability (NTCP) after exceeding the certain dose are also sigmoidal. The quantitative description of NTCP is much more difficult as it has to take into account not only the type of tissue (serial, parallel, or mixed organs) but also the type of complication. Also, non-uniform dose distribution in tissue must be considered. The NTCP curve is located to the right of the TCP curve. These curves must be located as far as possible from each other to obtain the best therapeutic effect while minimizing side effects. It allows achieving a maximum large therapeutic window. The location of the NCTP curve depends on the dose tolerance (TD) of the whole irradiated organ volume for the complication rate (q%), assuming that 1 means irradiation of the entire organ volume with the same dose.[34–36] The most commonly used NTCP model, so-called the LKB model (Lyman - Kutcher - Burman model) assumes that the dose of tolerance increases inversely to the power of the irradiated partial organ volume, which can be expressed by the equation:

$$TD(q, v) = TD(q, 1) * v^{-n} \quad (2)$$

It should be emphasized that in clinical practice, there are limited situations in which it can be determined that only the indicated volume of the organ has been given a specific dose. However, one can obtain a homogenous dose distribution in the target tissue, the dose distribution in normal tissue, despite the use of advanced radiotherapy techniques, is very heterogeneous. As already mentioned, TD and NTCP depend on the type of organ. Therefore, It should be emphasized that in clinical practice, there are limited situations in which it can be determined that only the indicated volume of the organ has been given a specific dose. However, one can obtain a homogenous dose distribution in the target tissue, the dose distribution in normal tissue, despite the use of advanced radiotherapy techniques, is very heterogeneous. As already mentioned, TD and NTCP depend on the type of organ. Therefore[34,36] both models assume that the probability of complications depends on the impairment of the physiological functionality of the whole organ as a result of damage to its chosen subunit. The organs are built of so-called functional subunits (FSUs) that function independently in a given tissue. In serial organs, FSUs are organized into a chain of connected units, so damage to one of them causes functional disorder in the others. Thus, the dose of tolerance, in this case, does not depend on the irradiated volume, but rather on the specific structure that absorbs the dose. In organs built in parallel, the critical element is the irradiation volume – up to a certain significant volume; the body functions can be taken over by other FSUs. The information on the type of organ structure is essential in terms of treatment planning. The type of organ building significantly affects the severity of side effects at the same physical dose.

Another model of NTCP analysis based on the organ type is the so-called Relative Seriality model developed by Kallman et al. This model defines a given organ in terms of its s̈eriality.S̈imilarly to the LKB model, attention is paid to the way of combining functional subunits and their size in the tissue/organ (i.e. tissue seriality). Based on the above, the relationship between the irradiated volume of normal tissue and the intensity of the radiation response is presented.[37] In this model, the s value is calculated, which determines how the subunits are combined in the tissue. The value of s is the quotient of the number of subunits (n) in a given tissue and the size of the subunit (m):

$$s = m/nm = 1/n. \quad (3)$$

The low value of the parameter s (0.003 – 0.02) indicates a parallel type of organ structure (e.g., lung, liver), while the value s = 1 indicates tissue composed of subunits connected in series (e.g., esophagus, spinal cord).[38]

The probability P of a radiation-induced tissue/organ damage with a serial connection of functional units (number of m subunits in a series) can be determined by the equation:

$$P = 1 - \prod_{i=1}^{m} (1 - Pi) \quad (4)$$

Therefore, the probability of occurrence of a post-radiation effect in the entire organ will depend on the radiation response of each of the serially connected Pi subunits.

If the organ is composed of sub-units connected in parallel, the probability of damage is expressed by the formula:

$$P = \coprod_{j=1}^{n} Pj \quad (5)$$

Radiobiological modeling of cardiotoxicity is particularly difficult for two main reasons. First of all, the heart was considered a relatively resistant organ. It was only in the last years that an increase in the survival time of patients provided data on cardiovascular complications after radiotherapy. Secondly, the heart is sympathetic to the organs in which the mixed way of joining the functional subunits comes in: serial – parallel, including the area consisting of many serial subunits (m) and connected in parallel (n). The probability of occurrence of NTCP in this type of tissues is described by the equation:

$$P = \coprod_{j=1}^{n} Pj \left[P = 1 - \prod_{i=1}^{m} (1 - Pi) \right] \quad (6)$$

5. Conclusions

The results published by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG),[39] which included 40 studies (20,000 women with breast cancer, subjected to long-term observation after adjuvant therapy with ionizing radiation and compared to a group of patients who were not subjected to radiotherapy) indicate that in the exclusion of causes of deaths other than cancer, 20-year survival rates were at 69.5 % in the radiotherapy group compared to 73.8 % in the control group. Analyzing the causes of deaths, it was found that they mostly result from cardiovascular diseases. In summary, it was noted that the overall improvement in survival in women receiving radiotherapy was only 1.2 % over 20 years of follow-up (37.1 vs. 35.9 %). Therefore, when planning treatment, one should try to save the heart as much as possible, otherwise, the beneficial results of radiotherapy in the form of increasing the percentage of survivals without disease will be lost due to the higher number of deaths due to cardiological reasons. Despite the improvement of planning and treatment techniques, still, in 5 % of patients treated in the 1990s, over 15 % of the heart volume was covered in the irradiated field.[19] Even when the heart is outside the field, it can receive about 1–2 Gy due to scattered radiation. Currently, there is no direct evidence of the danger of this dose; however, based on the studies of survivors of the Nagasaki and Hiroshima bombs, it was estimated that these doses might increase mortality rates due to heart disease by as much as 20–30 %.[40] It takes at least 10 years for myocardial dysfunction to be revealed clinically, so the problem of cardiac complications is likely to be particularly relevant in young patients. In their case, we expect

to get long-term survival and even cure of cancer. Atherosclerosis, which is the most common cause of heart disease, develops from the age of around 20 and progresses with age, but very rarely causes damage to the heart muscle in people under 40 years of age.

There are many epidemiological studies in the literature, not only regarding radiotherapy of breast cancer but also lung cancer, indicating the risk of cardiac complications after treatment with ionizing radiation. The response from the cardiovascular system to high-dose radiation is known and associated with a pro-inflammatory response. However, the effect of low doses may be completely different because it induces an anti-inflammatory response. Also, there is no unambiguous answer to the question of whether RICD is a deterministic effect. Radiotherapy in the area of the chest, especially in young patients, may be associated with the acceleration of the development of atherosclerotic and degenerative changes in the myocardium, which in turn will increase mortality from non-cancerous causes.

Moreover, there is a lack of literature data on the use of known radiobiological models to assess the risk of cardiovascular complications. The models described are general and concern any healthy tissue. Therefore, when planning treatment for patients, particular attention should be paid to the dose and area of the heart to be irradiated.

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Conflict of interest

The author declares that there is no conflict of interest.

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