ONLINE FIRST

REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY

ISSN: 1507-1367

e-ISSN: 2083-4640

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DOI: 10.5603/rpor.103525

Article type: Review paper

Published online: 2024-11-15

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Abstract

Background: The biological effects and clinical consequences of out-of-field radiation in peripheral organs can be difficult to determine, especially for low doses (0.1 Gy–1 Gy). In recent years, Monte Carlo (MC) methods have been proposed to more accurately predict nontarget doses. The aim of the present study was to assess the feasibility of using Monte Carlo methods to predict the biological response of tissues and critical organs to low dose radiation (0.1 to 1 Gy) based on results published in the literature.

Materials and methods. Literature review, including studies published by our group.

Results and Conclusions. It has long been assumed that radiation doses to peripheral organs located far from the target volume are too low to have any clinical impact. In recent years, however, concerns about the risk of treatment-induced secondary cancers, even in peripheral organs, have continued to grow in line with increasing life expectancy. At present, it is difficult in routine calculations to accurately determine radiation doses to the whole body and peripheral organs. Moreover, the potential clinical impact of these doses remains uncertain

and the biological response to low dose radiation depends on the organ. In this context, MC methods can predict biological response in those organs. Monte Carlo methods have become a powerful tool to better predict the consequences of interactions between ionising radiation and biological matter. MC modelling can also help to characterise microscopic system dynamics and to provide a better understanding of processes occurring at the cellular, molecular, and nanoscales.

Key words: Monte Carlo methods; biological response; out-of-field doses; dose calculation

Introduction

A large proportion of patients with cancer receive radiotherapy as part of their treatment protocol, with dose of up to 70 Gy or more. Although most of the radiation energy is deposited within the intersection of beams' paths and along the beam path, mainly in the target, body regions located outside of the target volume are also exposed to radiation — although at much smaller doses — due to the physical properties of radiation and the limitations of current technologies [1, 2].

Although the dose of ionising radiation is a well-defined parameter that can be measured and calculated, the response of living organisms to a given dose is more complex and more difficult to describe qualitatively and quantitatively. Assessment of the effects of radiation (both curative and adverse) requires in vitro and in vivo studies and clinical observation. The biological response to irradiation in vitro can be assessed by examining damage to the cells and cellular components. Response can also be assessed in vivo by observing tissue and organ function impairment.

Although it can be challenging to accurately assess biological response, the main factor driving response is the dose. In this regard, the response to radiation—both on the cellular level and in the whole organism — is much better understood at doses above a 1 Gy because deterministic effects make the radiation effects more visible and it is easier to trace tissue damage and/or impaired organ function. However, at doses < 0.1 Gy, the effects on the cellular functions are unclear. While cellular damage (e.g., DNA damage) caused by low-dose ionising radiation can be detected, it is much more difficult to predict how this damage influences the cell cycle and the cell's capacity to repair itself and continue dividing.

Wang et al. showed that low radiation doses (0.25 Gy) could lead to cell growth and gene transfer while doses > 1.5 Gy induced cell killing [3]. Those authors also showed that low dose radiation delivered prior to higher doses can attenuate the effect of those consecutive doses. This adaptive response to radiation is characterised by several effects, including activation of multiple signalling pathways, augmented DNA damage response, increased antioxidant function, and modulation of mitochondrial function [4].

The impact of radiation on DNA can be observed even at very small doses. For example, double strand breaks (DSB) begin to occur at doses as low as 1 mGy to 0.5 Gy. As the dose increases, the number of DSBs also increases, although this depends on the cell type [5]. The exposure of normal tissue to radiation doses > 0.5 Gy can induce persistent perturbations in molecular and cellular function [4]. High doses can cause irreparable DNA damage and negatively impact cell cycle progression [6]. High dose radiation can induce numerous alterations to macromolecules, severe modulation of cell signalling pathways, and degenerative/carcinogenic effects. For these reasons, it can be difficult to accurately describe the quantitative and qualitative response of cells, tissues, organs, and the whole body to radiation. In turn, this makes it difficult to confirm theoretical models.

In clinical practice, it is particularly difficult to determine the impact of low radiation doses (0.1–1 Gy) on peripheral organs. Although algorithms have been developed in an effort to estimate the biological response to such doses, including early and late effects and induction of secondary neoplasms, those algorithms are not sufficiently accurate [7]. Moreover, there is no agreed value for the dose to be taken as borderline to distinguish between stochastic/deterministic; dosimetrically measurable and non-measurable and, finally, being clinically relevant or not. In literature, depending on the point of view, 0.3, 0.5, 1.0, 1.5 or 3.0 Gy is used [8–11]. With this difficulty in mind, we set in our analysis a borderline at 1 Gy.

The aim of the present study was to assess the feasibility of using Monte Carlo methods to predict the biological response of tissues and critical organs to low dose radiation (0.1 to 1 Gy) based on results published in the literature.

Nontarget doses during radiotherapy

One of the guiding principles of radiotherapy is that the dose outside of the target volume (“nontarget dose”) should be as low as reasonably achievable (ALARA criteria). This is

important because nontarget radiation increases the risks of radiotherapy without providing any therapeutic benefit. According to Kry et al. [11], nontarget doses may be classified as either “in-field” or “out-of-field”. In-field radiation refers to the doses delivered to tissues that are not included in the treatment planning volume (TPV) but are located in the path of one or more radiation fields. In-field doses mainly originate from the primary radiation source. The out-of-field dose is defined as the radiation dose received by tissues located outside of the TPV and outside of all radiation fields. These tissues absorb secondary scatter radiation from the body, collimator, or other devices.

Physical processes leading to radiation dose in a body

Ionising radiation can be delivered in different forms, including electromagnetic waves (gamma or X-rays) or as particles that carry enough energy to ionise atoms. Electrons can break chemical bonds and as a result the cellular matter becomes ionised. While ionising radiation affects both cancerous and normal tissues, the risks of harming healthy cells can be mitigated by modifying the beam configuration during treatment planning. The absorbed dose refers to the energy that is deposited from ionising radiation due to interactions between the photons and particles, and the tissue.

Interaction of photons and high-energy electrons with structural elements of linear accelerator (shielding, target, flattening filter, collimators, multi-leaf collimators) might cause the creation of secondary particles, particularly neutrons (photonuclear effect) [12]. The fast (E_n > 10 keV) and thermal (E_n < 0.5 eV) neutrons may induce extra doses to patients during treatment [12-14].

Neutrons are significant contributor to the out-of-field dose for photon beams of 15 MV and their dose component is independent of the distance from the treatment field edge and is decreasing with depth in a body [15]. The most accurate technique to calculate the parameters of these secondary neutrons is the Monte Carlo technique [16].

Growing input of Monte Carlo simulation in dose determination during radiotherapy

The radiation dose is the key value that must be accurately known during radiotherapy. The dose can be calculated prior to treatment based on measurements and known interaction formulas. The dose can also be measured during radiotherapy. In any case, the dose must be determined with an accuracy of 3–5% [17], which is feasible for the dose from the primary

beam. This level of accuracy is sufficient to ensure tumour eradication and to accurately predict the early and late side effects in normal tissues. However, the situation in the peripheral body parts is more complex. The doses there are much smaller (0.1–1 Gy) and their exact determination is influenced by much more complicated processes due to the contribution of scattered radiation. From a clinical point of view, achieving the 3-5% level of accuracy is not important for these low doses, because 3-5% deviation will have neither clinical manifestation nor a significant effect on the cell viability. The reality is that in the peripheral body parts the dose uncertainty increases by tenfold while the does decrease to 0.1 Gy. Obviously, such low accuracy has virtually no clinical implications in altered cell killing. However, such a high uncertainty can modify the likelihood of inducing mutations, which are associated with these small doses and which can lead to carcinogenesis. At present, it is hardly possible to determine accurately low doses (up to 1 Gy) in peripheral organs attributable to scatter, particularly when using non-coplanar beams [18].

Dose can be measured using various types of detectors which can accurately measure the dose, but only if the calibration factors are known. It is substantially more difficult to measure radiation doses located outside the primary beam (out-of-field radiation) because the scattered spectral energy level is unknown and much lower than that caused by in-field radiation. As a result, there is no reference condition (no known calibration factor) that can be used for comparison with the actual measurement. This implies that it is much more difficult to accurately measure doses to peripheral organs that only receive scattered radiation [19].

In addition to ionisation chambers, several other detectors can be used to measure out-of-field radiation, including thermoluminescent detectors, semiconductor detectors, and radiochromic films. Certain types of detectors (i.e., ionisation chambers constructed using low-atomic number ($Z \leq 13$) materials, gafchromic films, thermoluminescent dosimeters) are much less dependent on changes in energy spectrum of radiation, thus, the determination of calibration factors for such detectors is associated with lesser error (over- or under-response to low energy radiation is less than 5–12%) [11].

The dose distribution is calculated prior to starting the course of radiotherapy. Several different types of algorithms (i.e., correction-based, model-based, and Monte Carlo) are used in computerized treatment planning systems (TPS).

The limitations of pencil beam algorithms in heterogeneous media are well known. These algorithms use a one-dimensional density correction, which does not accurately imitate the

distribution of secondary electrons in media with different densities [20–22]. These limitations can be overcome by using MC algorithms, a model-based dose calculation algorithm widely considered to be the most accurate treatment planning method. Although MC algorithms are more accurate than pencil beam algorithms, MC is a time-consuming method, which may make its use in routine clinical treatment planning impractical. Nevertheless, due to recent advances in computing capacity, the use of MC methods continues to grow.-

The convolution/superposition approach (model-based algorithm) is not specific for dose calculation in homogenous media, but it is clinically acceptable in heterogeneous media. The convolution algorithm requires a significantly shorter calculation time than the more accurate superposition method. In tissues with large inhomogeneities, the superposition method provides exact dose distributions in the target volume. The superposition method, a variant of the convolution method, can determine the dose with an accuracy that is only a few percent lower than that achieved by Monte Carlo methods, but an order of magnitude faster [23].

Due to the emergence of ever more powerful computers, Monte Carlo techniques are increasingly being used to perform dose calculations [24]. MC models may be particularly useful to calculate low doses in peripheral organs [25].

Our group has carried out several studies to investigate the feasibility of using Monte Carlo simulations for dose determination in peripheral organs [26,27]. However, assessing biological response with MC methods is much more complex [28].

The successful implantation of Monte Carlo methods to routine dose calculation and treatment planning is both a prerequisite and an incentive to use this approach also for simulation of normal organ and tissue side effects caused during radiotherapy [29].

Radiation-induced damages to be mathematically modelled

The dose is the main parameter that determines the clinical and biological (cells, tissues, organs, whole body) response to radiation. However, in addition to the radiation dose, other factors like cell cycle phase can significantly modify the biological effects of radiation. Consequently, many factors must be considered to accurately assess the effects of ionising radiation [4]. Numerous studies, including several by our group, have been carried out to better characterise the effects of ionising radiation in different situations, including the biological response to radiation in peripheral organs during radiotherapy, the involvement of

DNA damage repair mechanisms induced by various radiotherapy techniques (e.g., hypofractionated stereotactic body radiation therapy) [30] and cellular response measured in a quasi-humanoid phantom [31–33].

Even small doses can cause tissue toxicity leading to long-term complications, including secondary cancers (carcinogenesis). In organs, the damaging effects of radiation generally depend on tissue structure. During radiotherapy, doses > 0.5 Gy to healthy tissues can damage DNA, lipids, and endoplasmic reticulum. In turn, this damage may lead to cell senescence or death through apoptosis, mitotic catastrophe, necrosis, pyroptosis, and/or autophagy [34]. At lower doses (< 0.5 Gy), the probability of cell death is quite low and generally attributable to apoptosis or senescence. Nevertheless, low dose radiation can damage the DNA of surviving cells, potentially inducing dangerous mutations and, eventually, carcinogenesis [31].

Radiation damage to the DNA and the following erroneous repair can lead to gene mutations, frequency of which increases in proportion to the dose. However, these mutations are highly dependent on the cell type, the gene, and radiation quality. Some studies suggest that the frequency of mutations and genomic instability plateaus at radiation doses of 1 to 3 Gy [35]. Other studies have found that the number of mutations increases up to doses of 7 Gy [36], plateauing around 10–20 Gy [37]. For some genomic effects, the plateau can be explained by increased cell killing at higher doses [38].

Irradiation can induce cell death in a multifactorial manner, depending on the cell type, radiation dose, oxygen tension, and DNA repair capacity. Cell death, which is defined as the loss of replicative capacity (i.e., replicative or reproductive death), is usually measured in vitro by a clonogenic assay. The three major types of morphologically distinct cell death that are most relevant to radiation response are as follows: apoptosis (type I), autophagy (type II), and necrosis (type III) [39].

Although biological response can be assessed experimentally, it is difficult to do so with high accuracy [40]. MC methods take a different approach to assessing radiation effects, offering the potential for more accurate predictions of biological response. Many such MC approaches have been tested [41, 42]. The main challenge of predicting the biological response to ionising radiation is related to the uncertainty of the relative biological effectiveness (RBE). Empirical radiobiological models commonly used in clinical practice do not incorporate the radiation response of individual cells and do not predict the sensitivity of an individual tumour. However, such information could play an important role in response given that clinical data

suggest that even tumours of the same type can present vastly different responses to radiation due to differences in their molecular makeup. Unfortunately, models that include molecular markers are scarce, in large part due to the lack of parameters that link biological response to genetic pathways or tumour characteristics. Additionally, data quality is highly dependent on mathematical formulas, which means that large volumes of data are needed to fully parameterize empirical models. The complicated nature of biological response means that we must use population-based approaches, which have significant shortcomings and often result in dose under- or overestimation [40].

In contrast to empirical models, mechanistic models incorporate the underlying mechanisms of radiobiological response and include the known determinants of radiosensitivity (i.e., DNA repair processes and the cell cycle). More complex mechanistic models may be used to predict the role of genes involved in DNA repair without requiring extensive preclinical trials [43]. Some models appear capable of predicting radiation response based on cell phenotype or genotype characteristics, but more evidence is needed to confirm the predictive capacity of those models [44].

The biological response to low dose radiation is stochastic, which means that artificial neural network could potentially be used to predict the response in the complex setting of healthy tissues and organs. Objective methods are required for dose determination. However, numerous variables can influence biological response, which is why modelling methods, such as Monte Carlo or models based on artificial intelligence (AI), have been proposed [45,46]. Clearly, AI-based methods require large amounts of data. In this regard, collecting data on the biological response to low dose radiation in a simple setting would provide valuable information, but response still needs to be modelled in a more complicated setting (e.g., organs).

Monte Carlo codes used in radiobiology to predict biological processes in cells and tissues

Three approaches are used to simulate early DNA damage caused by radiation: 1) clustering algorithms, 2) explicit geometrical modelling of the DNA double strand and associated biological structures, and 3) a combination of the above. The clustering algorithm, developed by Francis et al. [47], is based on experimental data on DSBs and survival rates in GEANT4-DNA. Those authors simulated energy deposition from several types of radiation with the same linear energy transfer (LET), thus obtaining the ratio of clustered and single energy depositions for each type using the Geant4-DNA toolkit. Clustered depositions are especially

significant in terms of biological effects because they are more likely to produce multiple strand breaks, which are more lethal. Due to limitations in the physicochemical stages of simulation, another approach to simulation was developed. This approach uses a geometrical model of the biological target, with the DNA volume assumed to be cylindrical [48]. This model develops a high-resolution atomistic description (up to 30-nm chromatin strand) of the biological target [49]. The third approach — the mixed approach based on GEANT4-DNA — was proposed by Dos Santos et al. [50]. That model simulates direct damage from proton irradiation (range, 0.5–50 MeV) using a clustering algorithm to quantify potential single-strand breaks (SSB) and DSBs. Those authors found that the quantity and complexity of potential direct damage is higher in the nucleus of endothelial cells than in fibroblast cells, primarily due to chromatin condensation. Moreover, compared to alpha particles, proton irradiation induced more complex clustered damage. Meylan et al. [51] described the generation and management of complex DNA geometrical models by representing DNA as spherical volumes for the phosphate groups, the deoxyribose, and the bases. Based on the findings of that study, it is possible to calculate the direct and indirect DNA strand break yields for a primary particle [52].

Sakata et al. [25] found that the increase in LET due to the proximity of ionisation increases the DSB yield, which surpasses the SSB yield. In that study, the indirect SSB yield revealed a strong LET dependence; that is, the number of indirect breaks decreases as the LET increases. Compared to indirect SSBs, the number of direct SSBs is proportional to LET. The extent of DNA damage increases as LET values increase (> 40 keV/μm). The probability of direct SSBs after each simulation of the tracking of an incident particle can be calculated by assigning energy deposition to the closest strand molecule, with the probability of a break occurring being a function of the energy. An earlier study by that same group showed that indirect damage depends mostly on the probability of a chemical reaction between a hydroxyl radical and the sugar phosphate backbone, thus leading to SSB. It is expected that the GEANT4-DNA model will soon allow users to simulate indirect damage by merging the atomistic approach with radiolysis simulation [25].

The radiation-induced bystander effect (RIBE) also plays a role in the number of DSBs. RIBE depends on cellular communication (through gap junctions and secreted factors), by which irradiated cells spread radiobiological effects to neighbouring cells [53]. Given that RIBE can damage DNA, adding this process to simulations could be of value. The observed biological effects of RIBE, such as reduced cell survival and mutations, are due to DSB induction. The

Monte Carlo model developed by McMahon et al. [54] described the radiation response of cells by simulating their internal conditions (cell cycle, radiation damage, cell motility). Those authors used data from a study by Butterworth and colleagues who irradiated fibroblasts and prostate cancer cells in partially shielded flasks [55]. That in vitro experiment showed that RIBE mediates radiation effects to unirradiated cells and that it mainly contributes to cell response at low radiation doses (< 1 Gy). The aforementioned MC model developed by McMahon et al. [54] described RIBE as a soluble signal dispersing from irradiated cells through the medium. Based on that model, the authors showed that the bystander effect might significantly contribute to cell killing of uniformly irradiated cells at doses below 2 Gy (killing up to 80% at low doses).

The aforementioned examples show that Monte Carlo models can be successfully used to simulate complex molecular effects caused by different types of radiotherapy. Moreover, different models may consider different biological processes, depending on their target application.

Mathematical modelling has been applied in radiobiology since the 1920s [56]. Although the first models were relatively simple, over time, more reliable models of radiation-induced DNA damage have been developed. Monte Carlo simulation is a valuable method to understand and characterise radiation effects. As an example of a stochastic model, Monte Carlo methods allow for the visualization of radiation interactions on an event-by-event basis, including the tracking of scattering, excitation, and ionisation generated by the particles. This tool ensures modelling of radiation transport by simulating early events that induce DNA damage [57]. Monte Carlo methods used for these simulations include track structure codes, Monte Carlo damage simulation (MCDS) codes, and Geant4-DNA codes.

Track structure code

Radiation damage to biological structures at the DNA level can be evaluated by using dedicated MC codes known as track structure (TS) codes [41,58]. The specific spatial resolution of TS codes makes them particularly suitable to calculate energy deposition at molecular and subcellular levels for a wide range of energies, and to estimate clustered DNA damage and repair. TS codes provide detailed information about excitation and the energy released by atomic ionisation along the ionising particle's path. They can also simulate the process of free radical diffusion, which is crucial in the chemical stage of the radiation effect. In 1997, Nikjoo et al. [57] published a parameter study of mechanistic DNA damage

simulations. In that study, TS codes were used to calculate the initial DNA damage yields caused by low energy electrons (range, 100 eV – 4.5 keV). Diffusing hydroxyl radicals substantially contributed to DNA breakage.

Monte Carlo damage simulation (MCDS) code

Tracking codes are useful but time-consuming, which limits their application. Semenenko et al. [59] proposed a faster, quasi-phenomenological MCDS model as an alternative to the TS simulations proposed by Nikjoo et al. [58]. The re-parametrized algorithm can estimate cellular DSBs, SSBs, and multiple base damage. This model presents the total spectrum of damage generated by electrons, protons, α particles, and can provide detailed estimates of the number of lesions per gigabase pair. This model showed that the main difference between energetic electrons, protons, and α particles was the degree of lesion clustering. New MCDS parameter values can be used to estimate cluster yields for a wide range of particle types, kinetic energies, and oxygen concentrations [60]. In that study, the observations obtained by MCDS were in line with the TS simulations, which suggests that MCDS parameter values can help to characterise the relative effectiveness of radiation type, which is useful in particle-based cancer therapy. The authors concluded that the most complex, difficult-to-repair DNA damage occurs at the end of a charged particle's track, a finding that can also be useful for radiotherapy.

Geant4-DNA code

Geant4-DNA, an extension of the Geant4 MC code, is a promising tool for the radiobiological evaluation of DNA damage events and nanodosimetry [41]. Geant4-DNA, which was first released in 2007, has been applied to describe the interaction between electromagnetic particles and liquid water at the nanoscale [2]. The code has been improved by adding models of free radical production/diffusion and chemical processes, and can be used to simulate water radiolysis up to one microsecond after irradiation.

Several research groups have developed simulation codes to model ionising radiation damage to sensitive biological targets such as DNA molecules [61–63]. Geant4-DNA implementations include external beam radiotherapy, hadron therapy based on proton and heavy ions, radiotherapy using nanoparticles, and targeted therapies [7, 64].

In conventional models, DNA damage yield and lethality are estimated empirically. Consequently, there is a clear need to develop and improve these models. The inclusion of

bystander effect models can improve existing models, especially in the context of low dose radiation processes, as suggested by the developers of some MC models. For example, Douglass et al. [63] developed a stochastic MC cell death model that simulates the spatial distribution of ionisation events and clusters them into DSBs. This model also simulates the biochemical process of DSB repair. The model can predict individual cell death and thus the cell surviving fraction. Those authors developed an algorithm that clusters the ionisation events into two categories (simple or complex DSBs) present in each cell. This approach demonstrated that it was possible to accurately evaluate the radiobiological effects of different types of LET radiation on DSB formation. The two-lesion kinetic (TLK) model has been used to calculate cell survival probability for each cell in a geometric tumour, an approach that differs from standard calculations, which only calculate the average probability of cell survival. Douglass and colleagues [65] observed that the cell's capacity to effectively repair and overcome radiation-induced damage depends on several factors, including the volume of the nucleus occupied by the DNA, the ability of neighbouring DSBs to interact and cause lethal damage, and on the accuracy of repair processes.

Zhang et al. developed a new multi-scale MC model [66] to estimate radiation-induced cellular death in clinical radiotherapy. This model, which is based on the Geant4 code, performs simulations at various levels, ranging from the macroscopic (organs) to the microscopic (cells). Radiation damage is calculated at the cellular level. The repair process was modelled by an expanded reaction-rate, TLK model. The model was compatible with the linear-quadratic (LQ) model in terms of the relationship between the macro dose and radiation-induced cell killing. The modelled radiobiological effects demonstrated that low energy electrons had a greater dose effect, causing relatively more local cancer cell killing than higher doses. This type of low-energy radiation is found in gold nanoparticle (GNP)-enhanced radiotherapy, in which the probability of tumour control is increased by the presence of low energy electrons in close proximity to nanoparticles during irradiation [67]. MC methods can also be used to simulate the interactions of low-energy radiation particles. The energy spectrum is a pivotal factor in radiobiological mechanisms and can be used to identify volumes likely to respond better to an individualized, patient-specific treatment plan.

Relativistic Ion Tracks (RITRACKS) code

The Monte Carlo simulation code RITRACKS (Relativistic Ion Tracks) is used to simulate the radiation track structure of heavy ions and electrons [68]. The code simulates the energy deposition events and the position of all radiolytic species generated of all tracks in a pre-

defined irradiated volume. RITRACKS can simulate DNA damage at the atomic scale, DNA-associated proteins, and resulting DNA damage events. Using RITRACKS codes, Plante et al. [69] have shown how the histone protection is significant in the DNA damage process. They reported, that the presence of histones reduced the number of DNA breaks by about 50%. The breaks have been observed in the periphery of the nucleosome when histones were present.

PARticle TRACks (PARTRAC) code

The PARTRAC code is one of the most advanced track-structure tools [70, 71]. It is set up on cross-section databases for photons, electrons, protons and ions over wide energy ranges relevant for medical, biological and technical applications. The tool enables simulation of water radiolysis, diffusion and reactions of chemical species. Comparing with TS code, the PARTRAC is less accurate but considerably faster in calculating damages in structures [59]. The PARTRAC was used to reproduce both the physics of the passage of a particle inside the matter and the biological target (the DNA) at different spatial levels.

Artificial intelligence for Monte Carlo

Artificial neural networks can be used for deep learning and to simulate scattered radiation. Sarrut et al. [72] discussed the application of artificial neural networks for dose prediction. Neural networks might also be used to simulate biological response based on a dataset of results. The advantage of this approach is that no prior knowledge of the nature of these processes is necessary. MC methods are widely considered the gold standard for radiation dose calculations because they provide an accurate and highly detailed simulation of the physical processes involved in the interaction of radiation with matter. The radiotherapy TPS determines the optimal dose distribution needed to achieve the therapeutic goals while minimizing damage to surrounding healthy tissue. The division of treatment planning into knowledge-based, expert-based, and AI-based categories reflects the different approaches and technologies that can be used at this stage of radiotherapy. Combining AI-based treatment planning with MC dose calculations could provide a powerful framework to improve the accuracy and effectiveness of radiotherapy [73]. AI techniques, including machine learning algorithms, can be used to optimize treatment planning [74]. The integration of AI and MC methods in radiotherapy would increase the precision of dose calculations and the predictive accuracy with regards to biological response. Combining these two tools would streamline both planning and treatment, thereby ensuring better patient outcomes.

Conclusion

Until recently, radiation doses in peripheral organs located far from the target were not routinely determined as part of the planning process because it was assumed that low doses (0.1–1 Gy) were unlikely to have any adverse effects. Moreover, there is no clinical evidence to support the need for further treatment optimization, even in sensitive organs, such as the thorax, which can receive doses of up to 1 Gy during prostate irradiation.

Even if the doses in the entire body are known, the impact on clinical response remains uncertain. The biological response to low dose radiation depends on the organ. The response to low doses on the cellular level can be detected using experimental methods. DNA damage is the dominant mechanism by which ionizing radiation causes biological response. However, the determination of whether or how these cellular damages impair specific organ function remains not well evidenced. On the other hand, induction of secondary neoplasm has been extensively documented. Further study should investigate more in-depth the processes that occur within the range of 0.1–1 Gy and probably analyse these effects separately in smaller dose sub-ranges.

Monte Carlo methods can be used to predict response. Monte Carlo simulation is a potentially powerful tool to predict the consequences of interactions between ionising radiation and biological matter. These simulations can reveal the microscopic system dynamics and provide a deeper understanding of cellular, molecular, and nanoscale processes. We analysed different approaches to predict early DNA damage and application of various Monte Carlo codes. Monte Carlo methods are a highly promising tool for radiotherapy, offering the potential to more accurately predict the biological effects of low radiation doses in peripheral body parts.

Acknowledgement

The authors would like to thank Bradley Londres for professional language editing.

Conflict of interests

Authors declare no conflict of interests.

Funding

This work was supported by the National Science Centre of Poland under grant no 2019/35/B/NZ7/04342.

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