



Modeling of radiation effects to immune system: a review

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Abstract

Cancer metastasis is the major cause of cancer mortality and accounts for about 90% of cancer death. Although radiation therapy has been considered to reduce the localized cancer burden, emerging evidence that radiation can potentially turn tumors into an in situ vaccine has raised significant interest in combining radiation with immunotherapy. However, the combination approach might be limited by the radiation-induced immunosuppression. Assessment of radiation effects on the immune system at the patient level is critical to maximize the systemic antitumor response of radiation. In this review, we summarize the developed solutions in three different categories for systemic radiation therapy: blood dose, radiation-induced lymphopenia, and tumor control. Furthermore, we address how they could be combined to optimize radiotherapy regimens and maximize their synergy with immunotherapy.

Keywords Radiotherapy · Immunotherapy · Immune checkpoint inhibitor · Mathematical modeling · Machine learning · Outcome prediction

1 Introduction

Metastasis remains the cause of 90% of cancer death [1]. Radiation therapy (RT), on the other hand, is used to eradicate primary tumors as a local treatment, therefore it is often assumed to have no effect on non-irradiated metastatic tumors. However, there have been recent findings on the systemic effect of radiation [2, 3]. For example, the nude-mice lacking an immune system has been found to have little therapeutic impact of radiation [4]. In other words, immune system play a role to eradicate tumor in radiation therapy. Another example is known as the abscopal effect [5]. When there are both primary and metastatic tumors, the metastatic tumor is eradicated even if the radiation is delivered only to the primary tumor [6, 7]. Although the exact mechanism has yet to be determined, many researchers believe that the abscopal effect is due to the radiation effects to immune

system [8]. In other words, the radiation is hypothesized to play a role in antigen production [9]. However, the statement is against basic mechanism that we knew about radiation cancer therapy. The RT have been known to deliver energy transferred to destroy deoxyribonucleic acid (DNA), preventing cancer cells from proliferation [10]. Recent finding suggest that RT not only kills cancer cells by disrupting their DNA, but also has an effect on the immune system that aids in cancer eradication [2].

Recent successful clinical trials of immune checkpoint inhibitor (ICI) strengthened the arguments that RT may enhance the immune responses to tumor. In the PACIFIC trial [11], it was confirmed that when ICI (Durvalumab) was combined with radiation, the survival rate of non-small cell lung cancer patients was higher than when only radiation was utilized. The studies concluded that there would be a synergetic effects of combining radiation and ICI.

However, the immune system, specifically circulating lymphocytes in the blood, is known to be extremely sensitive to radiation [12]. In other words, even a small amounts of radiation dose causes a rapid reduction in the number of blood cells. For example, when the patient is exposed to radiation, it is common to experience the reduced number of lymphocyte counts after the irradiation [13]. Since the lymphocytes play a role in ICI therapy [14, 15], the ICI could

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be possibly ineffective when the number of lymphocytes is lower after RT. Accordingly, the recently published clinical trials show no improvement in response with the addition of RT to ICI [16–18].

In summary, the radiation is a double-edged sword for the immune system [2]. When cancer is exposed to radiation, it produces antigens and boosts the immune system. Radiation, on the other hand, impairs the immune system because lymphocytes are sensitive to radiation. If radiation is delivered appropriately to the tumor, then metastatic cancer can be eradicated with an aid of ICI. However, if immune system is overly damaged by radiation, not only the non-irradiated

but also the irradiated tumor control is not guaranteed in cancer treatment.

In order to maximize systemic antitumor response in RT, we separate the problem into three groups (Fig. 1):

1. Determine the radiation dose that has been delivered to the circulating blood
2. Predict the occurrence of radiation-induced lymphopenia
3. Predict the immune system's impact on tumor control.

We outline what approaches have been established to date and suggest what methodologies should be developed further for immune-saving radiation therapy.

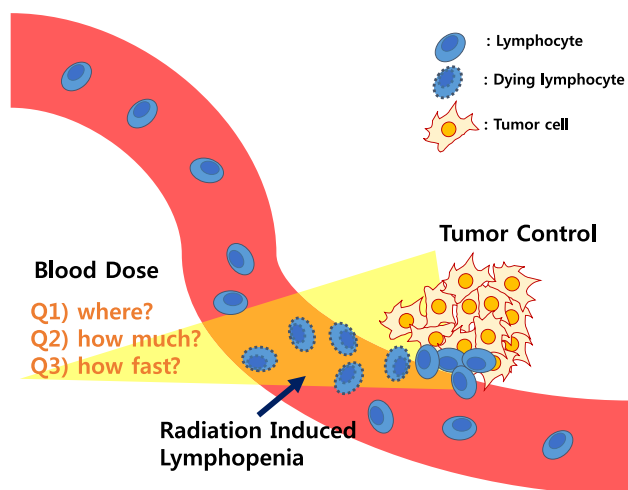


Fig. 1 Schematic of the parameters needed to build the model for the radiation damage to immune system

2 Blood dose

In modern radiation therapy, the various organs are considered as an organ at risk (OAR) to avoid the radiation dose, thus improve the quality of life for the cancer patients [19]. However, the immune-related organs such as circulating blood, lymph nodes, and bone are currently neglected as an OAR.

First thing we need to investigate is the radiation dose delivered to circulating blood, as summarized in Table 1. Various methods have been developed to calculate the blood dose in different perspectives: (1) macro-scale: population-based lymphocyte counts estimated under the appropriate assumptions and (2) micro-scale: individual lymphocyte explicitly computed in Monte Carlo method.

Table 1 Studies for modeling of radiation effects to immune system

| References | Patient cohort | Input factors | Predicted output | Summary of model architecture | Environment |
|---------------|---|--|-------------------------------|--|---|
| Yovino [20] | Single brain cancer patient | Dose to brain, dose rate | Blood dose | Probability | Matlab |
| Basler [21] | Single liver cancer patient | Dose to liver segments, dose rate, number of fraction | Blood dose | Convolution, Probability | Matlab |
| Jin [22, 23] | 456 non-small cell lung cancer (NSCLC) patients | Dose to body, heart, and lung, number of fractions | Blood dose, lymphocyte counts | Probability | Microsoft excel |
| Hammi [24] | Brain cancer patients | Dose to brain, dose rate, number of fractions | Blood dose | Markov chain + Explicit blood tracking | Matlab |
| Shin [25] | Brain and liver cancer patients | Dose volume histogram to 28 organs (ICRP 89) dose rate, beam delivery breaks | Blood dose | Markov chain | Python, Freely open source code to the public |
| Kim [27] | 84 Lung cancer patients | 3D dose distributions | Lymphopenia | Neural network | Python |
| Sung [29, 43] | 17 Hepatocellular carcinoma (HCC) liver cancer patients | Dose to liver segments, number of fractions | lymphocyte counts | Differential equations | Python |

2.1 Macro-scale: population-based lymphocytes

The macro-scale approach refers to treating circulating blood as a population group, instead of a sum of single individual cell. The computing cost is low, therefore calculation time is short. However, many physical/biological assumptions are included into the convolution / differential equation, hence the appropriate assumption should be carefully chosen.

Yovino et al [20] attempts to calculate the amount of radiation delivered to the circulating blood for brain cancer patients. The blood dose is estimated using the physical dose calculated to the brain as the input. It is assumed that the blood flows at a constant speed from inferior to superior region, and the dose in the blood vessel regions was added as a blood dose. The effects of altering the dose rate (MU/min) and dose per fraction to the blood are reported. The most important factor is found to be tumor size, because larger tumor size increases the irradiated volume in the brain.

For liver cancer patients, Basler et al [21] estimate the amount of delivered radiation dose to the blood. The eight separated hepatic segments are considered in the calculation. Their inputs are the dose volume histogram (DVH) of each hepatic segment and beam-on time. The blood DVH was convolved with hepatic segmental DVH for each fraction. The beam-on time, as well as tumor location and volume, are found to have a substantial impact on blood dose.

For lung cancer patients, the formula of effective dose to immune cells (EDIC) is developed based on a blood-flow continuity principle, reported by Jin et al [22, 23]. The advantage of the EDIC is its simplicity of using particular blood-containing organ for lung cancer patients. The EDIC model combines the mean body dose (MBD), mean heart dose (MHD), and mean lung dose (MLD) according to:

$$EDIC = 0.12(MLD) + 0.08(MHD) + \left(\left(0.45 + 0.35 * (0.85) * \left(\frac{\#offractions}{45} \right)^{\frac{1}{2}} \right) (MBD) \right)$$

2.2 Micro-scale: explicitly-calculated individual lymphocytes

The Monte Carlo method considers an individual blood cell as an object, and tracks its movement to determine the radiation dose received in the total blood group. The method can be generalized into other diseases because it eliminates several assumptions. However, their calculation speed is slow, compared to macro-scale method.

Hammi et al [24] developed a generalized whole phantom model and then used MRI scans to model the brain vessel in detail. Using the Markov chain, total $2 * 10^7$ blood particles are directly traced, and the difference in blood dose are estimated between proton and x-ray treatment plan. Proton therapy has a substantially smaller proportion of blood

volume receiving radiation dose after the first fraction with 10.1% compared to 18.4% in x-ray therapy.

Shin et al [25] expand the Hammi model [24] to include all other organs. The patient cases of brain and liver are further investigated. After a single radiation fraction, the volume of blood receiving any dose increases from 1.2% for 1 second delivery time to 20.9% for 120 second delivery time for brain cancer treatment, and from 10% (1 s) to 48.7% (120 s) for liver cancer treatment. It allows the amount of blood exposed to radiation be calculated quantitatively based on the dose rate. The code is released as open-source (<https://github.com/mghro/hedos>)

The concept of blood dose has two critical weakness.

First, the circulating blood dose is not measurable quantity. The dose delivered to other normal organ is also not easily measurable. However, there are several methods to attach a dosimeter to the patient surface or anthropomorphic phantom to estimate the dose to the internal organ indirectly. On the other hand, the measurement is limited for blood, because they are moving targets, which means the cell is traveling all around the patient internal organ. Also there is currently no techniques to attach the dosimeter to the single cell.

Second, the circulating blood is only one of the many immune organs in the patient body. The lymphocyte counts measured directly from the patient complete blood count (CBC) test are only the snapshot of the whole body. The number of lymphocytes is influenced by not only the circulating blood, but also the heart and other lymphoid organs such as nodes, spleen, and bone.

The developed methods still provide a solid physical dose calculation to the circulating blood. However, the methods in this section could be limited because they do not include

other biological factors such as dose-damage relationship and blood supply.

3 Radiation-induced lymphopenia

Radiation-induced lymphopenia is a condition in which a patient lymphocyte count drops faster than normal organs after radiotherapy. It is a measurable quantity, directly from the patient CBC test. Traditionally, it has been evaluated according to how low the lymphocyte count has dropped. The lymphopenia is defined as grade 1: absolute lymphocyte count (ALC) 800 – 999 counts/ul, grade 2: ALC 500–799 counts/ul, grade 3: ALC 200–499 counts/ul, grade 4: ALC < 200 counts/ul. The lymphopenia is one of the

quantity showing the damaged status of patient's immune system after radiotherapy.

Currently, three primary components are regarded as the significant sources to avoid lymphopenia: where (immune organ), how much (dose-damage relationship), and how fast (dose rate).

3.1 Where: immune organ

Which organs should we reduce the dose to avoid radiation-induced lymphopenia? Radiation therapy has traditionally been used to decrease the dose to the normal tissue by adjusting radiation intensity. However, for the immune system, where should we change?

Jin et al [26] estimate the damage to the immune system for the abdominal cancer patients. The immune system is categorized into five compartments (circulating blood, bone marrow, spleen, lymph node, and other tissue) with nine differential equations describing their interactions. The dose is assumed to be delivered uniformly in a normal serial-organ, while it is separately delivered to the normal parallel-organ.

Kim et al [27] investigates dose distribution and radiation-induced lymphopenia in 84 lung patients and 63 liver cancer patients. They find that pulmonary vessels and large hepatic vessels are important for lung and liver patients respectively. Further development of prediction model is also suggested using compact neural network integrating full 3D dose information directly with clinical data [27].

To avoid radiation-induced lymphopenia, current studies have shown the importance of designing a radiation treatment plan to avoid the lymphocyte-rich regions as much as possible. However, their cohorts are limited to single or two institutions. We propose the systematical recorded documentation across the multiple institutions to characterize a possible quantitative relationship.

3.2 How much: dose-damage relationship

Is there a linear relationship between the lymphocyte count and the mean blood dose? For other normal tissues, the concepts of LQ function and normal tissue complication probability (NTCP) were conventionally introduced to evaluate its damage – dose relationship with exponential and logistic function respectively [28]. Are those functions still applicable to immune system?

Jin et al [26] assumes that the circulating lymphocytes are subjected to the simple linear radiobiological model ($(\exp(-\alpha * \text{Dose}))$, α = radio-sensitivity constant (Gy^{-1})) instead of LQ model. The lymphocyte radiosensitivity is estimated to be $\alpha = 0.40 \text{ Gy}^{-1}$. The model is validated for the total 41 patients, and 21 among them have a sum of squared errors of less than 0.5.

Sung et al [29] describes the behaviors of circulating lymphocytes also as the simple linear radiobiological model. The framework describes not only the depletion and but also the recovery of lymphocytes with its supply and antigen recruitment. The model shows faster recovery of lymphocytes with short fractionation and less treatment breaks.

Instead of a mathematical model, Zhu et al [30] propose a hybrid deep learning model to predict the grade 4 radiation-induced lymphopenia as a classification problem. The model is trained from 505 patients with dosimetric (of heart, lung, and spleen) and non-dosimetric variables. Their model outperformed other predictive models (i.e., random forest, support vector machines, etc.) It achieved the highest area under the curve at 0.831 with robustness in exploiting the value of dosimetric parameters.

3.3 How fast: dose rate

What is the relationship between dose rate (Gy/second) and lymphopenia? Ultra-high dose rate (so called FLASH) radiotherapy has recently shown promising outcomes in normal tissue saving while conserving tumor control compared to conventional dose rate [31, 32]. Their research findings are also being analyzed to see whether the immune system plays a role in normal tissue saving effect [33].

Jin et al. [34] hypothesize that the FLASH-RT significantly reduces the killing of circulating immune cells which may contribute to the reported FLASH effect. Based on the developed lymphopenia prediction framework, the FLASH-RT is found to have a considerable sparing effect on circulating blood cells. Specifically, the death of circulating immune cells is reduced from 90% to 100% at conventional dose rates to 5-10% at FLASH dose rates.

4 Tumor control

The tumor volume shrinkage is a historical indicator correlating with better patient survival and clinical benefit [35]. The types of tumor control in radiation therapy are classified into local tumor control (in-field response) and systemic tumor control (out-of-field response) [3, 36]. In order to maximize the systemic tumor control of local radiotherapy, the radiation dose to the immune system should be minimized because the immune component such as lymphocytes plays a role inducing systemic tumor control.

Various methods have been developed to avoid radiation from normal organ, because reduced radiation dose to normal organ improves the patient's quality of life. For example, intensity modulated radiation therapy (IMRT) is found to reduce the xerostomia grade (a condition in which the salivary glands do not make enough saliva to keep mouth wet) [37]. On the other hand, the immune system as a normal

organ is important not only to improve the quality of life but also to control the tumor growth, even leading to better overall survival [38]. The role of immune system will be inevitably more important when combining ICI and RT.

The EDIC formula is gaining validity in different types of upper abdomen cancers. In stage III non-small cell lung cancer (NSCLC), Ladbury et al. [39] have published the correlation of EDIC and tumor progression. Xu et al. [40] and So et al. [41] also report its correlation with esophageal cancer after chemoradiotherapy with consistent finding. However, Thor et al. [42] show that the EDIC is not associated with progression free survival of the 113 NSCLC patients treated with combination treatments of chemoradiotherapy and durvalumab.

Sung et al. [43] develop a comprehensive framework for simulating the response to ICI in combination with RT and use it to investigate the ICI-RT combination regimen in liver cancer patients. The suggested framework successfully describes the tumor volume trajectories as in monotherapy clinical trial. It is found that the irradiated tumor fraction is the most essential metric for the success of the ICI-RT combination regimen. Adding RT to ICI boosts the clinical benefit from 33 to 71% in non-irradiated tumor sites, when 90% of the tumor cells being irradiated.

5 Limitations and future perspective

Although ALC is the best-studied predictive immune biomarker in patients with cancer undergoing radiation therapy, other lymphocyte subsets should be integrated into the modeling. The lymphocyte is a highly heterogeneous cell population consisting of subsets with different roles in the interactions with tumors. The CD4+ T cells, for example, support other blood cells in producing an immune response, whereas CD8+ T cells directly kill tumor cells. Moreover, the radiosensitivity may vary depending on their subsets. For instance, CD8+ T cells are more radiosensitive than memory T cells. The subset information of circulating lymphocytes will be further required to refine the model based on clinical patient data, resulting in a better knowledge of tumor-immune interaction and improved model prediction performance.

In metastatic setting, systemic therapy is the main treatment whereas in locally advanced cancer, systemic therapy is usually given concurrently with radiation therapy. Many studies report effects of systemic therapy on lymphocyte counts during the therapy itself, with a consensus that chemotherapy reduces circulating lymphocyte levels [44, 45]. Therefore, not only the radiation- but also the chemotherapy-induced lymphopenia should be systemically modeled to derive optimal combination regimen.

Pre-treatment patient variables also affect the severity of lymphopenia. Recent study finds that higher age and lower body mass index (BMI) are predictors of grade 4 radiation-induced lymphopenia [46]. For example, a physiologic reasoning for their finding could be that a higher BMI implying larger blood volume relates to greater lymphocyte reserve. Therefore, not only the interventional radiation-related parameters in this review, but also the pre-treatment parameters can be helpful to stratify individual patients suitable for lymphopenia-mitigating strategies.

6 Summary

Immunotherapy are reorganizing modern cancer treatment. Conventional radiation therapy is expected to be also transformed into immune-saving radiation therapy [47]. Cancer patients with lymphopenia are expected to have poor treatment outcomes in the clinical research [38, 48–50]. The current challenges and opportunities are the developments of accurate and reliable normal tissue complication probability models to predict the lymphocyte depletion. In this review, we point out the three key players in immune-saving radiation therapy: dose, beam-on time, and radiosensitivity. In addition, the irradiated tumor fraction and treatment sequence should be carefully selected in ICI and RT combinations. Immune-saving radiation therapy is not only able to improve tumor control [51], but also possibly reduce the risk of COVID-19 death in cancer patients [52].

We strongly encourage investigators in clinical trials to systematically record the potentially-relevant dosimetric and hematopoietic parameters. We also recommend medical physicists to be engaged in clinical trials, because they are well-trained medical professionals in dealing with complicated systems. A patient-specific treatment plan for immune-saving therapy could be achievable, eventually through the correctly designed clinical trial.

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