Integrating mathematical modeling into the roadmap for personalized adaptive radiation therapy

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Abstract

In current radiation oncology practice, treatment protocols are prescribed based on average outcomes of large clinical trials, with limited personalization and without

adaptations of dose or dose fractionation to individual patients based on their individual clinical responses. Predicting tumor responses to radiation and comparing predictions against observed responses offers opportunity for novel treatment evaluation. These analyses can lead to protocol adaptation aimed at the improvement of patient outcomes with better therapeutic ratios. We foresee the integration of mathematical models into radiation oncology to simulate individual patient tumor growth and predict treatment response as dynamic biomarkers for personalized adaptive radiation therapy.

Main text

State of the Art in Radiation Oncology

Radiation Therapy (RT) (see Glossary) is the single most commonly delivered oncologic treatment, and is utilized in over half of all cancer patients at some point in their care [1,2]. In the US alone, this amounts to more than half a million patients per year treated with radiation therapy [3]. RT is commonly given with curative intent as monotherapy, or in combination with surgery, chemotherapy or immunotherapy, or in the palliative setting [4]. In breast cancer, for example, adding irradiation to breast conserving surgery significantly reduces the cumulative incidence of recurrence [5,6]. RT induces DNA damage that, if not repairable, leads to cell death. If DNA damage is mis-repaired, cells may die during subsequent division attempts or accumulate potentially deleterious mutations that reduce cellular fitness. With the large number of cancer cells in clinically observable human tumors (1 cm^3 of tumor is generally believed to contain about 10^{7-8} cancer cells [7]), large **radiation doses** are required to sterilize all cancer cells. However, to limit normal tissue radiation-associated toxicity, RT is usually **fractionated** into smaller doses to give surrounding non-cancerous tissues opportunities to recover between treatment fractions.

For most cancers, different doses and dose fractionations have been and are actively being prospectively evaluated [8]. Advances in physics and delivery techniques have led to the ability to sculpt radiation dose distributions to more accurately hit planning target structures and lower doses to adjacent organs at risk based on medical imaging. This allows delivery of larger doses per fraction, and ushered in the era of

hypofractionation (large doses per fraction in fewer treatments and shorter overall time) and stereotactic ablative body radiation therapy (SABR) or stereotactic body radiation therapy (SBRT). SABR and SBRT deliver large doses of precise radiation, often given in as few as one to five fractions, to the tumor with limited exposure to healthy tissues [9]. The recent phase 3 CHISEL trial showed superior local control without increase in toxicity of SABR (18 Gy x 3 fractions or 12 Gy x 4 fractions) versus standard fractionated radiotherapy (2 Gy x 25 fractions or 2 Gy x 33 fractions) in stage 1 non-small-cell lung cancer [10]. Fewer, larger doses may also harness synergy with the patient's immune system. Pre-clinical studies suggest that radiation dose fractions of 8-12 Gy may induce strongest antitumor immunity [11,12] – observations that have yet to be confirmed in prospective clinical trials.

One Size does not Fit All

Many radiation protocols have been and continue to be derived from average outcomes of large clinical trials and long-term empirical practice, resulting in a "one size fits all" approach for most tumor types. Prescribed total radiation dose, anatomical dose distribution and dose fractionation are based on **maximum tolerated dose** (MTD) concepts independent of patient-specific biology. While for certain indications total dose may be based on tumor size and normal tissue limitations, there exists no explanation for why two patients with similar histology, primary site, and clinical stage would have different tumor responses and therapy outcomes. Reliable biomarkers and quantitative modeling frameworks based on individual tumor/host features and microenvironmental conditions are needed to personalize total dosage, dose fractionation and **dose painting**. Biomarkers that help treatment response predictions will allow evaluation of

clinically observed responses to intensify or adapt therapy for patients predicted to fail standard RT, or to de-escalate RT and reduce potential RT-associated toxicities when possible without sacrificing cure. Traditional biomarkers have shown promise in multiple treatment settings, but many have shown to be not predictive or prognostic. It is conceivable that the actual value of a putative biomarker may not be as insightful as the rate at which the biomarker changes over time before and during therapy. Instead of static readouts of variable biology such as TNM stage (tumor volume, lymph node involvement, and metastatic burden) or genomic expression profiles [13,14], the dynamical system that is underlying tumor growth dynamics and changes in putative biomarkers may be formally described and evaluated by mathematical models [15]. We foresee mathematical models being calibrated and validated with radiobiology and radiation oncology data to help forecast patient specific tumor growth dynamics and treatment responses. Indeed, we see the future of cancer staging as moving from the current static model where patients are assigned once an initial stage, to a time when staging becomes a dynamic and evolving variable which better predicts a patient-specific outcome.

Integrated Mathematical Oncology

Cancer biology, clinical oncology, and mathematical modeling have existed in parallel for many decades. Several mathematical and statistical approaches have been used to better understand complex biological systems and to predict biological responses to therapy. Most prominently in radiation oncology are the widely used Linear Quadratic (LQ) model [16], Biologically Effective Dose (BED) [17,18], Tumor Control Probability (TCP) [18], and Normal Tissue Complication Probability (NTCP) models [19], as well as

novel genomic adjusted radiation dose (GARD) calculations [20]. Similarly, radiation biological questions have motivated the development of elegant mathematical models [21–24]. Yet, to fully harness the synergy of mathematics and oncology, an integrated, iterative approach is needed. Biomedical questions and available data drive the development, calibration and validation of mathematical models to specifically help answering these questions, to test hypotheses, and to generate new hypotheses for subsequent experimental or clinical evaluation [25–28]. In a pioneering pre-clinical study, an experimentally calibrated mathematical model was able to predict an innovative radiation dose fractionation schema that indeed improved overall survival in a PDGF-driven glioblastoma mouse model [29]. The next steps of translating and evaluating such novel mathematical model-derived treatment protocols from mouse to human are underway (NCT03557372 [i]).

The past few years have seen the dawn of an area where mathematical models are being translated into prospective clinical evaluation. Based on the LQ model emerged the concept of temporally feathering radiation exposure to organs at risk (OAR) (NCT03768856 [ii]) [30]. Radiation sensitivity and repair dynamics of non-cancerous tissues may allow to deliver a larger dose to an OAR once a week, while a lower dose is delivered the other four days. A mathematical model suggested that this new treatment technique could decrease overall radiation-induced toxicity to feathered OARs, or be used to increase the total dose to the tumor if needed without additional OAR toxicity compared to standard RT plans. With the same aim of reducing OAR toxicity, a NTCP-based approach has been recently proposed to select patients that would benefit from proton therapy rather than photon therapy [31,32]. Although this method has already

been adopted by the Dutch Health Council and the Dutch Health Care Insurance Board, efforts are still needed to collect clinical radiobiology data for including routine morbidity assessments and further evaluation of the NTCP-thresholds in the selection criteria, and to find optimal models that balance data fit and predictability [33]. In a different study, pre-treatment tumor growth dynamics and relative tumor volume inform a mathematical model to calculate a proliferation saturation index (PSI). PSI is proposed to predict response to different radiation fractionations, thereby allowing patient-specific stratification into once daily or twice daily protocols (NCT03656133 [iii]) [34,35].

Predicted tumor growth and treatment response dynamics to evaluate clinical responses

Pre-treatment tumor growth dynamics have been shown to be predictive and prognostic in glioblastoma [36] and oropharyngeal cancer [37]. In addition to correlating untreated tumor dynamics with treatment outcomes, the ability to predict volumetric regression during therapy brings the opportunity to revisit response evaluation criteria in solid tumors (RECIST [iv] [33]). Current RECIST stratifies tumor responses during treatment into complete response (CR) if there is no radiographic evidence of disease (NED), partial response (PR) if the sum of diameters of the target lesions has decreased by more than 30%, progressive disease (PD) if the sum of the diameter of the target lesions increases by more than 20%, and stable disease (SD) otherwise [38]. RECIST compares observed responses against the pre-radiation volume – a static measurement that ignores tumor growth dynamics and the time from treatment initiation. Radiographic increases in tumor diameter of 20% by week one should be evaluated differently than a 20% diameter increase by the end of RT. It is conceivable that during the 5-7 weeks of

RT the tumor volume increases by 25%, yet untreated tumor growth would predict significantly larger volumes. Despite lack of tumor volume reduction, substantial deviation from the untreated growth trajectory could be considered robust response (**Figure 1A**). Similarly, tumors that are dormant, i.e. not increasing in volume prior to therapy and thus at stable disease, should be considered non-responding if stable disease is observed (**Figure 1B**). This has prompted discussions about mathematical modeling and computer simulation-derived response metrics, such as '*days gained*' [39,40]. *Days gained* calculates the time between predicted tumor progression *after* therapy with predicted tumor progression *without* treatment. For the illustrative examples in Figures 1A and 1B, *days gained* would offer a more adequate radiation response evaluation than RECIST.

Toward integrated adaptive radiotherapy

One major shortcoming of current radiation schemes is the open-loop control approach (**Box 1**), where total dose, anatomical dose distribution and dose fractionation are chosen based on pre-treatment state [41]. Patients with similar TNM stage are prescribed with the same radiation protocol without regard to inter-patient heterogeneity in tumor growth dynamics, cancer biology and radiobiology that may determine treatment outcome [14,42]. Cancer is a complex adaptive dynamic system, and such systems are best understood when analyzing the temporal response to perturbations. Radiation therapy is arguably a significant perturbation to the untreated tumor and its microenvironment, and treatment response may offer invaluable insights into possible tumor composition, radiosensitivity, and evolutionary dynamics.

The concept of closed-loop control (**Box 1**) is the adjustment of treatment plan parameters based on systematically monitoring system variables [43]. Current adaptive radiotherapy exclusively adapts the target volume based on radiographic changes [44], or escalates the dose to more aggressive tumor areas identified on mid-treatment PET/CT [45]. The main objective of radiation therapy is to eradicate the gross tumor volume (GTV), and longitudinal GTV measurements are readily obtainable from positioning imaging integrated into modern linear accelerators, e.g. cone beam computed tomography (CBCT), MRI, or CT or MRI on rails. Based on radiographic response, it is conceivable that treatment plan parameters such as total dose, anatomical dose distribution and dose fractionation could, and possibly should, also be adapted. For non-responding tumors, these dosing variables may be modified in a variety of ways (higher total dose, higher dose per fraction or unique dose distributions in the target) to potentially produce a better outcome. On the other hand, dose de-escalation in responding patients may reduce radiation-associated side effects without compromising cure. For more insights into response, higher order **radiomics** such as shapes, textures, or habitats may introduce actionable triggers for treatment adaptation [3]. Additional biological response dynamics may be obtained from molecular imaging or circulating tumor DNA in liquid biopsies [46–48].

As response evaluation may be informed by tumor dynamics prior to and during therapy (Figure 1), an adaptive control loop in radiation oncology may need to be based on a predictive mathematical reference model (**Figure 2, Key Figure**). Pre-treatment growth

dynamics, either alone or in combination with molecular biomarkers of radiation sensitivity, may inform mathematical models to predict responses to specific radiation schemes. Observed tumor responses can then be evaluated against model prediction, and deviation of prediction and observation may be the trigger for radiation protocol adaptation. When observed volume reduction is less than predicted, radiation dose may be intensified or fractionation adapted toward accelerated, **hyperfractionated** or **hypofractionated** schemes [34]. For some selected patients with exceptional responses, treatment adaptations may also allow for dose de-escalation to limit radiation side effects without sacrificing cure. The prediction model itself may be dynamic and iteratively improved as new observed response data become available to decide whether treatment needs to be updated [49]. Mathematical and computational modeling may be uniquely positioned to guide treatment adaptation through patient-specific phase *i*, virtual *in silico* trials [50,51]. Informed by early individual patient response dynamics, different treatment protocols can be simulated forward in time to identify personalized optimal dose and dose fractionation for the remainder of the treatment plan (**Figure 2, Key Figure**). This may include counterintuitive decreasing dose-per fraction for poorly responding tumors [34,35]. Computer simulations of potential treatment adaptations may also include adding or removing chemotherapy [52], immunotherapy [53] or surgery [12] toward a truly multidisciplinary patient-specific adaptive therapy.

Concluding remarks

With increasing understanding and evidence of inter-patient heterogeneity, cancer therapy should be tailored to individual patients. While the flood of genomic data has thus far occasionally affected the decision for use of chemotherapy and certain targeted biological agents [54], it has yet to impact radiotherapy. The limiting factor of precision medicine based on genomics remains to the lack of temporal resolution and, thus, the inability to inform treatment adaptation based on response. In the era of artificial intelligence (AI) in medicine, machine learning may also have applications in radiation oncology beyond image segmentation, treatment planning and motion detection [55]. However, machine learning approaches remain a 'black box' and are not positioned to provide mechanistic insights and unable to make predictions outside the data used for training. In addition to AI, we are also witnessing the advent of integrating mechanistic mathematical modeling into radiation oncology with the goal to understand tumor growth and treatment response dynamics. Mathematical models have made inroads into clinical trials to evaluate their ability to support clinical decisions; the next step has to be to implement closed feedback loops to adapt treatment based on predicted and observed responses, which may require a closer integration of quantitative scientists to complement the clinical care team (see outstanding questions).

Mathematical model outputs for each individual patient to adapt total dose, anatomical dose distribution and fraction sizes in radiotherapy are testable in prospective clinical trials. The major hurdle will be to collect, store and share patient-specific data to train mechanistic mathematical models (see outstanding questions), and to link, calibrate, and correlate the differences in the model predicted and observed tumor volumes with

the necessary changes in radiation dose and/or dose fractionation after every iteration around the closed-control loop.

While tumor volume is currently used to evaluate response, medical imaging provides data that are currently underutilized [56]. Higher order radiomics features of the tumor and its microenvironment, conceivable first or second order patterns or hidden features to be revealed by AI approaches, may further shed light onto the spatio-temporal tumor heterogeneity and biological responses. These may ultimately be harnessed to handle the varied and heterogeneously responding tumor ecosystem, such as increased dose painting to hypoxic or radioresistant areas and reduced radiation to habitats of immune infiltration on a per patient basis.

Resources

[i] https://clinicaltrials.gov/ct2/show/NCT03557372

[ii] https://clinicaltrials.gov/ct2/show/NCT03768856

[iii] https://clinicaltrials.gov/ct2/show/NCT03656133

[iv] http://recist.eortc.org/recist-1-1-2/

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389

Glossary (450 words)

Fractionation. Total radiation dose is divided into smaller doses (fractions) that are given over a longer time frame to enable healthy tissues and organs at risk within the radiation field time to repair radiation-induced damage.

Hyperfractionation. Delivery of smaller radiation doses more frequently, including multiple treatment fractions per day.

Hypofractionation. Delivery of larger radiation doses less often.

Integrated mathematical oncology. Integrated mathematical oncology is a novel approach to synergize expertise in mathematics, engineering, physics, and computer science into cancer research and clinical oncology. In close collaboration, experimental and clinical data inform quantitative models to perform simulations of tumor growth and treatment response dynamics. Model predicts are subsequently evaluated experimentally and clinically.

Maximum tolerable dose. Cancer treatment is based on the concept that more is better, including radiation with radiation survival significantly decreasing with dose. Phase 1 clinical trials are commonly dose escalation trials to determine the maximum dose that can be tolerated without dose-limiting toxicities.

Radiation dose. Radiation dose with unit Gray (Gy) defines the absorption of energy (unit Joule) in tissue, with 1 Gy = 1 J / kg.

Dose painting. Delivery of spatially heterogeneous radiation doses based on radiological imaging features.

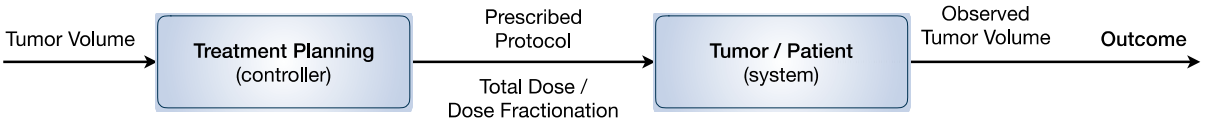
Radiotherapy / Radiation oncology. Radiation oncology treats cancer using radiation, which deposits energy in the cancerous tissues to induce DNA damage. Unrepaired or mis-repaired damage will lead to cell death.

Radiomics. Radiomics is the study of images as data. Images contain patterns beyond the composite image that can be rigorously analyzed.

Box 1. Radiation therapy as adaptive control problem

Open-loop control; treatment plan based on pre-treatment information

Control problems are common in engineering, and different control strategies can be directly translated to cancer therapy. A complex dynamic system needs to be controlled with specific actions that are based on measurements of the system (input). In current open-loop control approach, contoured CT, PET/CT, or MRI images are used to develop the technical radiation plan for each patient. Based on the TNM stage, a specific total dose and dose fractionation treatment plan is deployed to the tumor, which results in the new state of the system (tumor eradication, tumor control, or tumor progression).



Closed-loop control; treatment plan adaptation based on information prior to next fraction

In a closed-loop control approach, the state of the system is evaluated after each action during the control process to change the controller based on response (adaptation loop). In radiation therapy, the tumor volume can be evaluated at time of radiation delivery (treatment fraction), and the technical plan (gross tumor volume, target volume) or treatment plan (total dose, dose fractionation) can be adapted to changes in tumor volumes for subsequent fractions (dose escalation; hyper- or hypofractionation).

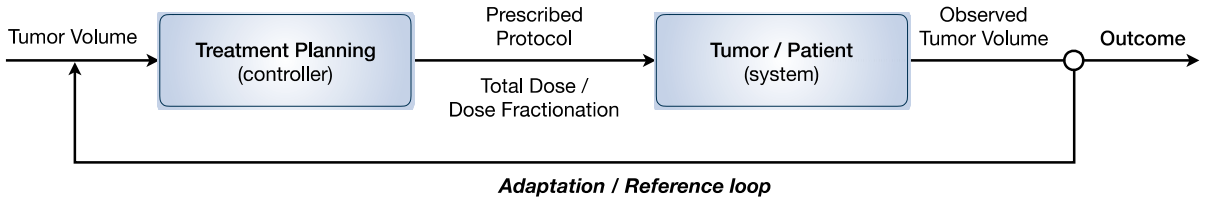


Figure 1. Illustrative examples of pre-treatment tumor growth dynamics, predicted response and observed responses. dx: diagnosis. (a) Pre-treatment tumor growth dynamics predict untreated tumor volumes that show response despite observed progressive disease (PD). (b) Observed stable disease (SD) should be classified as no response if tumor growth was dormant prior to treatment and no changes to tumor volumes are predicted without radiation. (c) Clinically observed partial responses may be considered poor response if pre-treatment tumor growth dynamics predict complete response (CR).

Figure 2, Key Figure. Proposed adaptive radiation therapy using integrated modeling. The observed tumor volume is compared to the *in silico* predicted tumor volume after the prescribed treatment dose and dose fractionation (reference model). If treatment needs to be adapted, mathematical models can be trained with observed response dynamics and alternative protocols be simulated *in silico* (reference model 2). The predicted optimal protocols for the individual patient can help inform dose and/or dose fractionation adaptation.