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REVIEW ARTICLE

# Current status and future developments in predicting outcomes in radiation oncology

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## ABSTRACT

Advancements in data-driven technologies and the inclusion of information-rich multiomics features have significantly improved the performance of outcomes modeling in radiation oncology. For this current trend to be sustainable, challenges related to robust data modeling such as small sample size, low size to feature ratio, noisy data, as well as issues related to algorithmic modeling such as complexity, uncertainty, and interpretability, need to be mitigated if not resolved. Emerging computational technologies and new paradigms such as federated learning, human-in-the-loop, quantum computing, and novel interpretability methods show great potential in overcoming these challenges and bridging the gap towards precision outcome modeling in radiotherapy. Examples of these promising technologies will be presented and their potential role in improving outcome modeling will be discussed.

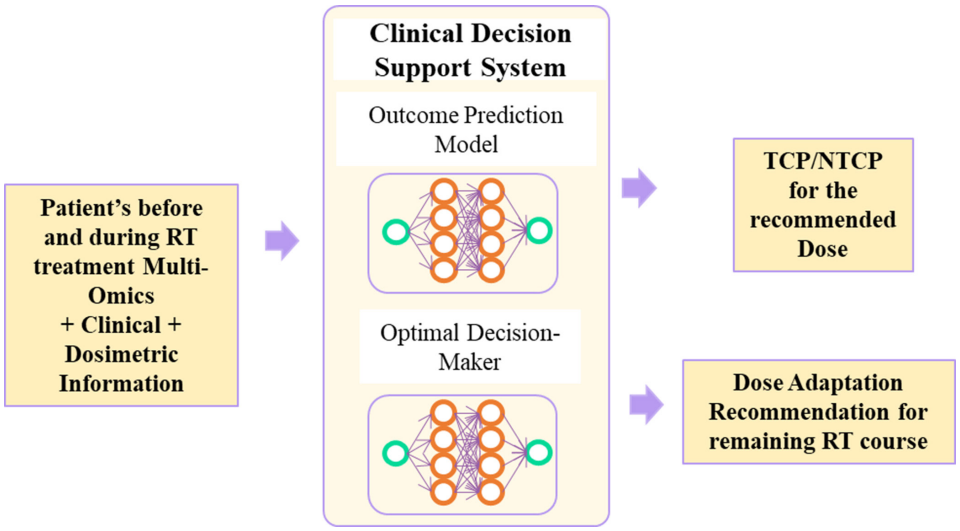
## INTRODUCTION

The past decade has witnessed rapid advancements in data-driven technologies that have influenced virtually every field in medicine including treatment response modeling and outcomes prediction in radiation oncology.[1–10] Advanced big-data analytics have facilitated the integration of information-rich multiomics data with the traditional clinical and dosimetric information for modeling radiotherapy (RT) treatment responses.[11,12] Inclusion of such multiomics information, which is the aggregation of genomics, proteomics, transcriptomics, metabolomics, epigenomics, and radiomics, among others, as prognostic or predictive biomarkers has improved the potential of such outcome models in personalizing treatment management and achieving the promise of precision medicine in radiation oncology.[13–16] These improvements in data and algorithmic modeling performances can be attributed to the enhanced ability to capture underlying cancer heterogeneity caused by subtle interhuman genetic and physiological differences. The inclusion of multiomics data can effectively improve the representation of patient-specific radiosensitivity beyond traditional dose–volume metrics used for modeling the observed tumor control probability (TCP) and/or normal tissue complication probability (NTCP), which have dominated the field of radiation oncology over the past decades.[17]

Traditionally, outcome prediction models (OPMs) in RT have relied on a simplistic representation of dose response using analytical models such as the linear quadratic (LQ) model. Though such models are useful for understanding the dose–volume effect at a population level and has been used for fractionation conversion purposes in RT treatment planning, they have limited ability to address treatment management requirement at the patient level. In the modern era of precision medicine such one-hat-fits-all approach is not acceptable anymore.[18]

Towards meeting the requirements of precision medicine, modern OPMs are envisioned to be utilized in constructing semi- or fully automated clinical decision support systems (CDSS) that could be applied for personalized and adaptive radiotherapy (ART).[19,20] Such a CDSS is depicted in Figure 1. In this case, the CDSS evaluates patient's dose

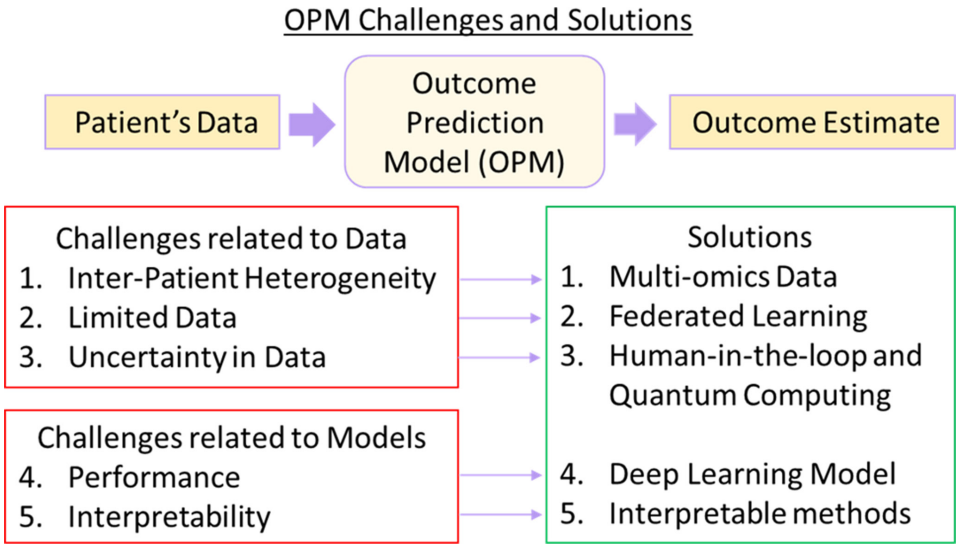
Figure 1. CDSS for ART.[19] CDSS is composed of OPM and ODM. Given a patient's before and during treatment multiomics, clinical, and dosimetry information, the OPM outputs corresponding TCP and NTCP. ODM recommends an optimal dose adaptation value for the remaining treatment course. ART, adaptive radiotherapy; CDSS, clinical decision support systems; NTCP, normal tissue complication probability; ODM, optimal decision maker; OPM, outcome prediction model; TCP, tumor control probability.




response by analyzing trends in patients' multiomics biomarkers measured before and during treatment, which are fed into an appropriate OPM for projecting outcome estimates. The CDSS then can recommend an optimal dose adaptation value for the remaining treatment period that will maximize the observed TCP and minimize the observed NTCP. This recommendation could be made via a sequential decision-making algorithm such as deep reinforcement learning. Note that in modern era of OPMs, the notion of TCP/NTCP is generalized from simplistic dose–volume metrics into more comprehensive multiomics patient-specific approach that utilizes artificial intelligence (AI) as its computational vehicle.[21,22]

It is recognized that advanced data-driven approaches fueled by AI-based machine and deep learning (ML/DL) techniques have significantly improved the predictive power of OPMs. However, researchers have been actively working on overcoming two main impending challenges related to data and algorithmic modeling. This will further enhance OPM's utilization and crossing the bridge of so called the 'AI chasm' that separates development from clinical implementation.[23] Figure 2 summarizes the data modeling related challenges of interpatient heterogeneity, limited data set, and high level of uncertainty in data, and the algorithmic modeling related challenges of model performance, uncertainty, and model interpretability.

Figure 2. The current challenges and actively researched solutions in OPM in Radiation Oncology. OPM, OPM, outcome prediction model.



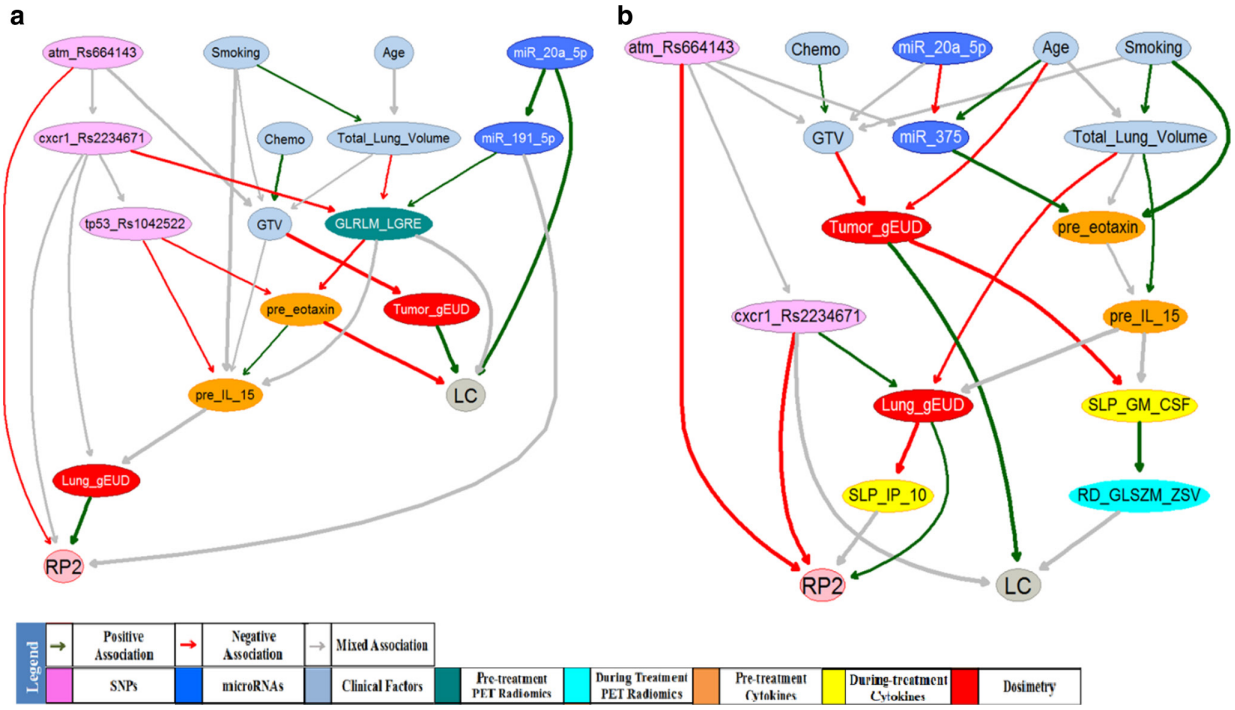
Accessibility of sufficiently large data sets and availability of noise-free data required for clinical-grade robust model development and evaluation are currently lacking. While the underlying reasons are not mutually exclusive, the former issue, which creates a barrier for implementing ML/DL big-data analytics, is associated with a set of privacy laws established for protecting patient's rights.[24] The latter issue arises from several reasons including missing data, measurement error, and interpatient heterogeneity. Currently, researchers have been actively involved with federated learning (FL) to tackle the sample size requirements issues, and application of human-in-the-loop (HITL) learning & quantum computing to overcome the uncertainty issues. Additionally, preventive measures such as standardizing the data acquisition and data harmonization methods are other actively ongoing efforts for improving the data quality for outcome modeling.[25]

FL[26] is an emerging paradigm in the fields of ML/DL algorithm development in which OPMs are trained across multiple decentralized servers, located in multiple institutes. The advantage of FL is that at one hand the data doesn't need to leave the premise of the institution. On the other hand, this paradigm provides the necessary sample size for accurate and robust statistical modeling while protecting the data privacy.[27,28] While there are numerous works on FL in other fields, it is an active area of research and development in radiation oncology[29] and in the medical field in general,[30–34] mainly because, unlike ML/DL platforms (*e.g.* pytorch or tensorflow),[35] the infrastructures for FL are still lacking. Jochems et al,[36] in their proof-of-concept study, developed a tool for survival prediction of non-small cell lung cancer (NSCLC) patients treated with chemoradiation or RT that was trained in data set located in two different cancer institutions and then further validated the model in another institution. Those institutions were located in three different countries in two different continents.

HITL[37–39] is a hybrid of data- and knowledge-driven approaches that integrates prior expert knowledge into ML frameworks. The synergy between machine and human intelligence helps to alleviate model uncertainty, improve model trust level (credibility), and build upon current understanding as opposed to starting from scratch. Luo et al[40] have implemented HITL for NSCLC OPM, where a Bayesian network architecture was applied to a multi omics dataset for making predictions of local control (LC) and radiation induced lung inflammation (pneumonitis (RP)) as shown in Figure 3. The study integrated known biophysical interaction between the patient features into modeling without which the task would have been extremely difficult and prone to uncertainty given the limited sample size and a large feature size. Similarly, Sun et al[41] have designed a new framework for integrating expert human knowledge with AI recommendations for optimizing clinical decision-making in ART in lung cancer.

Quantum computing and quantum information theory[42,43] are a natural fit for dealing with data uncertainty, stochasticity, and noise. In addition, application of quantum information can significantly speed up computation compared to its classical counterpart. Because of its advantages, quantum computing has been applied to ML algorithms[44] and with the rapid development of quantum computing platforms, quantum ML algorithms are actively being researched.[45–48] Niraula et al[20] have modeled clinical decisions as quantum states to represent the uncertainty

Figure 3. Multiobjective Bayesian Network prediction reproduced from Luo et al.[40] Pre-treatment (a) and during (b) treatment HITL-BNs for joint prediction of LC and radiation pneumonitis Grade two or above (RP2) are shown in this figure. The is an example of OPM that takes in multiomics data from before and during treatment. HITL, human-in-the-loop; LC, local control.



faced by physicians in decision-making during RT treatment. The uncertainty in decision-making mainly arises due to the availability of partial information on patient's state and due to the uncertainty in treatment outcomes. In another example of application of quantum computing, Pakela et al[49] demonstrated that quantum tunneling based annealing optimization techniques can optimize intensity-modulated radiotherapy treatment plan much faster than the traditional simulated annealing optimization method. A faster optimization algorithm would permit in reoptimizing a treatment plan in a shorter time frame during the treatment course to account for changes such as tumor shrinkage and organ deformation to optimize the treatment outcome.

Aside from data-related issues, the interpretability of advanced predictive ML/DL models is also a concern to the medical community.[50–53] DL models, in particular, are popular for their high degree of accuracy. However, because they are complex non-linear models composed of up to billions of parameters with non-convex objective functions, interpreting DL models is not always easy. In general, complex models trade-off accuracy for interpretability. Usually, complex models are regarded as a black box, whose architecture (hyperparameters) are optimized with respect to the task in hand and are utilized without delving deeper into the how's and why's. While such practices are usually acceptable in non-medical fields, medical conservatism emphasizes the need for interpretable models as an acceptable clinical tool due to safety issues and legal compliances. Researchers in radiation oncology are integrating interpretability methods into their predictive models. Wei et al[54] implemented an integrated gradient method for identifying the important radiomics features from a DL model trained for risk prediction of overall survival in hepatocellular carcinoma patients.

We begin this review with an overview of the traditional mechanistic predictive outcome models, primarily based on the linear quadratic model for estimating TCP and NTCP. Then, we present the current status of predictive modeling, which is mainly focused on the inclusion of multiomics patient-specific information followed by a CDSS framework that leverages such multiomics based OPM for optimizing RT treatment plans. We finish with a discussion on the current challenges and limitations of predictive modeling associated specifically with the AI data-driven technologies and actively sought out solutions that could potentially overcome the current gap (AI chasm) that separates development from clinical implementation.

## BASIC OVERVIEW

Two major types of clinical end points considered in outcome modeling are TCP[55] and NCTP.[56] TCP is defined as the probability that a tumor is eradicated or controlled after receiving a certain amount of dosage and NTCP is defined as the probability of radiation-induced normal tissue toxicities that an organ of interest may exhibit after exposure to unwanted radiation. TCP-related end points may include LC, regional control, etc. NTCP-related end points are more diverse and may vary among disease sites.[57–61] Note, in our description, below we are using TCP/NTCP in their generalized sense as comprehensive OPM with multiomics patient-specific input data.

Conventional analytical outcome models are mainly based on dosimetric and volumetric information. These models may formulate the outcomes according to simplified radiobiology theory or available dosimetric data to a parametric model. Many analytical (mechanistic and/or phenomenological) models have been proposed in the literature.[62] Here, we present a brief description of the common analytical outcome models used in the clinical treatment planning software.[18] For the interested reader, more in-depth analysis of these models and their application can be found in[62]

TCP modeling: The well-known linear-quadratic (LQ) model and its variants are based on irradiation effects observed from *in vitro* cell culture experiments. In a LQ model, the logarithm of survival fraction (SF) of cells is composed of both linear and quadratic terms of the physical dose, relating to lethal damage caused by the 'single-hit' and 'multiple hit' events, respectively. It is possible to use the LQ model to convert the size of fractionation dose while keeping an iso-effect of the biological response for the end point of interest. The biologically effective dose (BED) concept could be used to convert dose under different fractionation schemes to a standard fractionation scheme. For instance, a quantity called EQD2 is a special case where dose under different fractionation schemes is converted into equivalent total dose given in 2 Gy per fractions. TCP models can be also built by fitting empirical data, for instance, logistic regression can be adopted to associate dosimetric variables to TCP.[63]

NTCP model: The Lyman model[56] is a well-known NTCP model, which uses a cumulative Gaussian distribution to fit the toxicity events of interest,

$$NTCP\left(D, D_{50}, m\right) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{1}{2}u^2\right)\, du,$$

where,

$$t = \frac{D - D_{50}}{mD_{50}}.$$

Here, $D$ could be represented by the generalized equivalent uniform dose (gEUD), $D_{50}$ is a dose uniformly irradiating the whole organ that relates to 50% NTCP, and $m$ is a parameter that controls the slope of NTCP. Additional parameters regarding the volume effect can be further incorporated if the dose distribution is inhomogeneous. Other sigmoidal functions, *e.g.* logistic function, log-logistic cumulative distribution have also been applied to model NTCP.[64]

Note that the TCP and NTCP models differentiate between tissue types via a radiosensitivity parameter denoted as the $\alpha/\beta$ ratio. This ratio is central to BED and EQD2 estimation and to subsequent calculation of both TCP and NTCP models. In practice, the $\alpha/\beta$ ratio is not well characterized for all tissue types, including organs at risk (OARs), which can introduce additional uncertainty in the TCP and NTCP modelling process.[65]

Predictability of the conventional analytical OPM is limited to the dosimetric information. OPM can be improved by basing it on other information such as imaging and multiomics data.[66]

However, due to the sheer number of feature size, hand crafting an analytical model is very difficult, if not impossible. Thus, data-driven techniques such as statistical and ML have been utilized for OPM.

In the general sense, outcome modeling can be typically defined as a supervised learning problem in the context of ML.[67] A mapping function from patient-specific information to the end points of interest can be learned using the training data. Then, this function can be applied to an unseen data set to infer clinical end points for a given input, patient-specific data. Outcome modeling could be presented as a classification problem when a pre-set of cut-off thresholds is used to determine the end point. Otherwise, an outcome model can apply to predict the probability of events directly using regression techniques. The combination of growth in patient-specific multiomics data, complexity of radiation response process, and advances in ML algorithms, particularly the success that DL algorithms that have demonstrated in the field,[68] have led to the burgeoning interest in applying ML/DL methods to outcome modeling in RT.[62]

### Current status of outcome modeling in radiotherapy

Currently, many treatment planning systems still utilize analytical models based on the LQ models and its variants as add-ons which may or may not be consulted during planning. The focus remains on meeting dose–volume physical constraints rather than achieving desired outcomes based on radiobiological models. This is primarily due to uncertainties associated with these models, their population-based nature, and the scarcity of proper optimization methods that could utilize such models.

Recently, there has been extensive efforts and advances made in personalizing outcome modeling for RT. It is recognized that outcome prediction in radiation oncology is multifactorial and involves correctly identifying patients' radiosensitivity of tumor cells and surrounding healthy cells. Identifying radiosensitivity,[69] however, is not an easy feat, because it depends on many dynamic factors such as tumor heterogeneity, tumor volume, hypoxia, cell damage repair, cell cycle, etc., that can change over the treatment period. Moreover, radiosensitivity differs from patient to patient. A possible way to include patient-specific radiosensitivity in outcome modeling is by integrating patient-specific multiomics information.

Advancements in imaging acquisition technologies have gifted us the field of radiomics in which large-scale imaging information can be incorporated into modeling RT responses. Currently, there are two areas associated with radiomics, one is based on hand crafted features (*e.g.* morphology and texture) and the other utilizes raw images directly using DL.[70] Moreover, measuring and quantifying molecular biomarkers, such as gene expression microarrays and RNA sequencing methods, and data-driven techniques that can process large amount of genetic data, have transformed the predictive modeling landscape from a population based one with limited predictive power into a data-driven one that allows for individualized treatment management with ML modeling.

Advanced ML/DL models can now leverage before and during radiation treatment information on patient's relevant radiogenomics biomarkers that are extracted from tumor biopsy, blood work, and imaging radiomics, to capture the intrinsic heterogeneity and accurately incorporate patient-specific radiosensitivity in OPM. For instance, Luo et al[14,15,71] showed improvement in prediction accuracy by including multiomics information of NSCLC patients as predictive biomarkers for LC and RP. They analyzed hundreds of biophysical features including dosimetry, clinical, pre- and during treatment cytokines, miRNAs, as well as single nucleotide polymorphisms (SNPs), and selected the most important features for predicting the outcomes. They then developed an OPM based on Bayesian Networks that presented the causal relationship between the features and the outcome. Similarly, Cui et al[13] developed a DL-based prediction model that jointly predicted LC and RP in NSCLC patients. Patient-specific information including differential dose–volume histograms, PET tumor radiomics, and biological information were input into a composite deep neural network. The composite architecture was able to learn the representation of features and perform the prediction task simultaneously.

Tseng et al[19] designed a deep reinforcement learning-based framework for CDSS in ART. By inputting patient's state information, comprised of important multiomics features, the CDSS can recommend an optimal dose fractionation. In that work, for a given state and an amount of dose fractionation, an artificial radiotherapy environment that was constructed out of OPM could predict a patient's resulting state and corresponding treatment outcome. By using that environment, a deep reinforcement learning network was trained to recommend optimal dose fractionation that would maximize TCP and minimize NTCP. Niraula et al[20] have further advanced the work by improving the model of artificial radiotherapy environment. They integrated prior knowledge on dosimetric features into the OPM and combined neural networks with mechanistic models to ensure that the dosimetric features respected the radiological physical requirements, *i.e.* the gEUD values increased with increasing dose fractionation and both TCP and NTCP values increased with increasing gEUDs. Future modeling processes will witness increase in data types as well as integration of prior expert knowledge into data-driven methods. Additionally, deep reinforcement learning methods have also been used for precision oncology,[72] 2D tumor growth simulation-based dose fractionation,[73] and beam reshaping via multileaf collimation for real-time adaptive RT.[74]

## FUTURE DEVELOPMENT

In addition to prospective evaluation, the following challenges needs to be addressed.

1.Overcoming limited data

1A. Federated Learning

The curse of dimensionality, as coined by Richard E. Bellman, demands an exponentially large sample size for a high dimensional data set.[75] This occurs since the volume of the feature space

expands rapidly with the increase of the feature dimensions, which means that to be able to gain from high-dimensional data sets such as multiomics, we will need information from exponentially more patients. The small sample size to feature size ratio is even more pronounced in the medical field where data points are sparsely distributed and limited due to ethical and legal issues associated with human experimentation. To make the matter worse, data-sharing in healthcare is strictly regulated due to privacy and patient protection concerns. FL can aid in overcoming these data access limitation issues and has been actively pursued by the medical community including radiation oncology.

In FL, data do not leave the secure confinement of the data owner's firewall but let a foreign model securely access the data and learn from it. Several network topologies have been proposed for FL, such as centralized, decentralized, hierarchical, hybrid hierarchal, etc.[27] For instance, in a centralized topology, a central server broadcasts multiple identical models to distant data servers which allows the models to access their local data set. The local models then calculate local loss function and send it back to the central server. The central server then collects the local loss functions and then aggregates it in a weighted fashion where the weights are selected according to the characteristics of the respective data sets. Then, the model is updated in the central server and the updated models are again broadcasted for another iteration. Models trained under FL have shown to achieve comparable performance to the ones trained under traditional centralized ML.[76–78]

FL has many other benefits such as overcoming selection bias due to accessibility of data from a wide range of regions and demography, the ability to perform comparative studies of subgroups of patients that might have different radiosensitivity, high quality ML aided tool for diagnoses and outcome predictions, etc. There are also concerns and challenges, such as having to deal with heterogenous data sets that are not independently and identically distributed (non-iid) due to interinstitutional differences in RT clinical protocols, data acquisition methods, and differences in computing hardware resources. However, considering the current momentum and early success of the ongoing research, it is safe to be optimistic about the prospects of FL.

2. Overcoming uncertainty issues

In the domain of radiation oncology, data are usually collected under heterogenous conditions that lead to a noisy data set. There can be many sources of data noise such as interference, calibration error, sparse data set, small data set, measurement error, discretization, batch effect, intrinsic heterogeneity in humans, etc.[79] A significant degree of uncertainty can arise from record-keeping related issues, such as inconsistencies and difficulty in classifying radiation induced toxicities and reporting outcomes, even with a standard Patient-Reported Outcome Measures (PROM's) questionnaire. Any data-driven outcome model based on a noisy data set will have larger prediction uncertainty. Another source of uncertainty in RT comes from clinical decisions. Since physicians must prescribe decisions without a complete knowledge of confounding patient's dose response factors, their decisions may have a high degree of uncertainty which gets propagated into the recorded clinical data. Currently, there are ongoing research efforts in the following two areas for dealing with data noise and modeling uncertainty.

2A. Human in the loop

Being rooted in reinforcement learning, preference learning, and active learning, HITL is a hybrid of data-driven and knowledge-driven approach that overcomes model uncertainty by integrating prior expert knowledge into ML frameworks.[80] Holzinger et al defined HITL as "algorithms that can interact with both computational agents and human agents to optimize their learning behavior through these interactions.[81]" HITL approach can reduce the complexity of a hardest decision-making problem (NP-Hard) through assistance of a human agent in the learning phase.[81] Furthermore, experimental evidence for the utilization of HITL algorithm has demonstrated that human intelligence can positively augment machine intelligence.[82]

The concept of HITL has been intensively used to tackle obstacles created by data-related limitations. By exploring human–machine partnership with AI, Patel et al demonstrated that AI-based technology achieved superior accuracy than the human experts alone in chest radiograph diagnosis.[83] In other study of HITL for interplaying between digital image analysis (DIA) and pathologists, Boden et al found that HITL corrections could address major DIA errors in terms of poor thresholding of faint staining and incorrect tumor-stroma separation for individual cases.[84] In OPM for NSCLC, Luo et al implemented HITL learning for creating a causal graph of feature and end points via Bayesian network architecture. The OPM took in multiomics data set for making predictions on LC and RP as shown in Figure 3.

As ML/DL plays an increasingly important role in medical image analysis, the integration of HITL and ML/DL becomes even more necessary for designing CDSS. Budd et al evaluated four key areas to improve the integration in clinical practice: active learning for the best data selection, interaction with model outputs for models steering, full-scale applications before deployment, and the evolvement of knowledge gaps to benefit HITL computing.[80] However, it is still unclear how to design optimized relationships between people and machines in a scalable manner, how to design triggers for proactive engagement and disengagement, and how to handle the consequences of implied interventions. The verification of treatments in a large HITL machine medical system can be very complex due to its evolving nature from both patients' aspects and the clinical environment. Therefore, it is critical to understand human–machine interaction semantics and control for the behavioral context in designing OPM with HITL.[85]

2B. Quantum computing and information theory

Quantum computation, built on quantum information theory, is intrinsically indeterministic, making it a natural medium for modeling noise and uncertainty. Unlike digital computers, where

a value is deterministically represented by a collection of bits, a quantum system represents a value as the mode of a probability distribution. By representing the data as a quantum state, we are modeling the noise by the spread of the distribution. Furthermore, by carefully designing quantum ML algorithms,[86] we can model the interaction between the patient's state and the radiation dose, which would automatically encapsulate the propagation of uncertainty and naturally present the outcome prediction with an uncertainty metric. Researchers are working on such a complete quantum model.

Recently, Pakela et al[87] designed a hybrid quantum deep recurrent neural network (RNN)-based OPM for predicting tumor volume and daily setup changes in head and neck cancer patients. Just as it is impossible to predict the behavior of a quantum system with absolute certainty, there are inherent uncertainties in knowing a patient's "state" during RT due to physiological changes such as tumor response and anatomical motion as well as limitations in cone beam CT (CBCT) image quality. The OPM modeled the combined patient tumor volume and daily setup changes as a stationary quantum state whose time points were discretized by the number of fractions. The authors demonstrated that such a hybrid model could perform almost as well as the classical Markov-based model. The performance, measured in AUC scores, of the predictive Markov model compared to the hybrid quantum model, evaluated in an external validation data set, were 0.707 *vs* 0.623, 0.687 *vs* 0.608, 0.723 *vs* 0.669, and 0.697 *vs* 0.609 for patient's discrete states sizes of 4, 6, 8, and 10, respectively.

Hybrid quantum algorithms have also been explored for beamlet-weight optimization in intensity modulated radiotherapy (IMRT) treatment planning. Pakela et al[49] developed a hybrid optimization algorithm by merging annealing and quantum tunneling. The quantum tunneling annealing optimization schedule reached convergence up to 46.6% faster than traditional simulated annealing algorithm for beamlet intensity optimization and up to 26.8% faster for direct aperture optimization.

Quantum computing can also be used to model decision-making. Niraula et al[20] designed a hybrid quantum deep reinforcement learning algorithm that modeled human decisions as an indeterministic quantum state. By training the framework in IBMQ quantum computer, they demonstrated the feasibility of the quantum framework as a CDSS which can potentially aid physicians in the clinic. Following a self-evaluation metric based on the retrospective clinical outcome, they showed that a decision-support system based on their framework can potentially improve the clinical decision by 10%.

3. Model interpretability

Making accurate prediction requires utilization of complex models with many parameters. However, complex models are difficult to interpret precisely. This trade-off between accuracy and interpretability is troublesome especially in high-risk fields such as radiation oncology. On the other hand, without fully understanding the relationship between the features and the outcome prediction, it is very hard to differentiate authentic relations from artifacts. Therefore, currently, extra effort is being put into developing interpretable models and tools for model interpretation/explanation. Interpretable graph networks such as Bayesian networks are being actively applied for outcome modeling which can trace the internal relationships between the features and their combined relationship with the outcome. Interpretability tools are also being actively developed and incorporated into outcome prediction models that are built on black-box type models such as tree-based and deep learning models.

Several methods are available for interpretation that can be categorized into model-agnostic methods such as feature importance, sensitivity analysis via input perturbation, local attention mechanisms, Shapely values, etc., and model-specific methods such as feature visualization, saliency maps, adversarial examples, etc.[88] Model-agnostic methods are especially desirable because they can help in comparing different models based on the feature to outcome relationship. Model-specific methods, especially in the context of neural networks, are desirable to extract learned features from the hidden layers and are usually much faster than the model-agnostic methods. Saliency mapping tools such as Decovnet, Grad-CAM, Guided Grad-CAM, and SmoothGrad are popular interpretation tools for CNNs and have been applied in radiomics and imaging in radiation oncology.

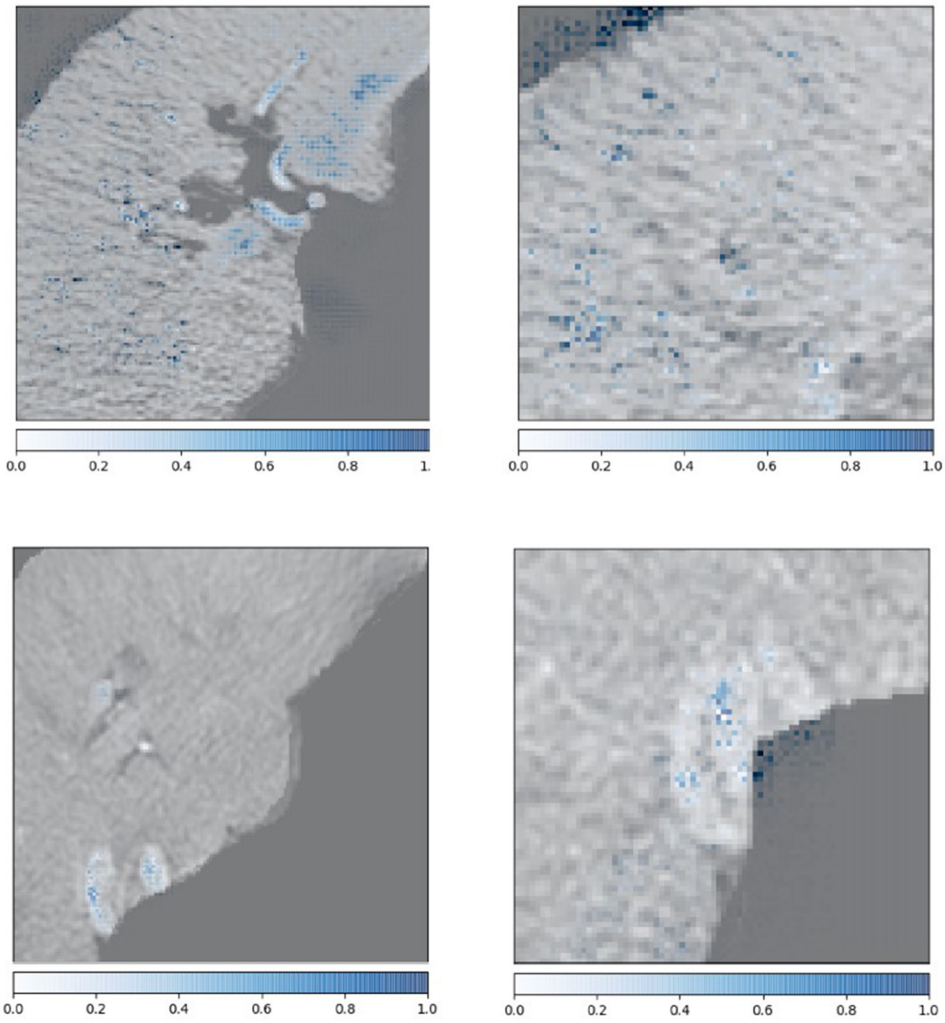
Liang et al[89] developed a CNN-based prediction model for RP that utilized dose distribution as an input feature. There, the authors used Grad-CAM[90] to locate regions of the dose distribution that strongly correlated with the positive and negative cases of RP. Similarly, Cui et al[13] applied Grad-CAM method to provide insight into what was learned by the composite model and thereby increased their model's interpretability.

Wei et al[54] applied a combination of variational autoencoders (VAEs) and CNN to identify a new radiomics signature using imaging phenotypes and clinical variables for risk prediction of overall survival in hepatocellular carcinoma patients. The model included two VAE survival components for the clinical and radiomics features and a CNN survival network for the contrast-enhanced image input. For model interpretation, integrated gradients methods were applied which helped in identifying the clinical liver function and liver exclusive of tumor radiomics features as the top-ranked features for risk prediction. An example image showing the interpreted outputs using integrated gradients is shown in Figure 4. Normal liver tissues were given more attention by the model for high-risk patients, which is consistent with the fact that top-ranked features were liver-GTV texture features.

## CONCLUSION

Currently, predictive modeling in radiation oncology utilizes patients' multiomics information along with the traditional dosimetry and clinical information. Automated decision-support systems for adaptive RT have been developed utilizing multiomics-based predictive modeling. The current data-driven OPMs performs better than their traditional mechanistic models due to enriched patient-specific information. However, data

Figure 4. Liver-GTV images marked with blue patches from integrated gradient methods. Top row shows the images for a patient with GLN 0.756, died in 264 days. Bottom row shows the images for a patient with GLN 0.154, survived 760 days (right censored). The blue dots are the output of integrated gradients method that shows the critical pixels for the prediction of the neural network which provides a direct explanation on how the deep learning-based outcome prediction model classified the images.




modeling-related issues have been hindering the deployment of these models to achieve their full potential. Significant effort is being made to overcome these issues with a combination of emerging technologies such as FL, HITL, quantum computing, and novel model interpretation tools that were highlighted in this review. Prospective evaluation of OPM is necessary for clinical application.

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