Data Science Opportunities To Improve Radiotherapy Planning and Clinical Decision Making

Joseph O. Deasy, PhD

Department of Medical Physics, Attending Physicist, Chief, Service for Predictive Informatics, Chair, Memorial Sloan Kettering Cancer Center, New York, NY.

Abstract

Radiotherapy aims to achieve a high tumor control probability while minimizing damage to normal tissues. Personalizing radiotherapy treatments for individual patients, therefore, depends on integrating physical treatment planning with predictive models of tumor control and normal tissue complications. Predictive models could be improved using a wide range of rich data sources, including tumor and normal tissue genomics, radiomics, and dosiomics. Deep learning will drive improvements in classifying normal tissue tolerance, predicting intra-treatment tumor changes, tracking accumulated dose distributions, and quantifying the tumor response to radiotherapy based on imaging. Mechanistic patient-specific computer simulations ('digital twins') could also be used to guide adaptive radiotherapy. Overall, we are entering an era where improved modeling methods will allow the use of newly available data sources to better guide radiotherapy treatments.

Radiotherapy aims to optimize the ratio between tumor eradication probability and normal tissue toxicity probabilities. This requires selecting the best dose distribution and the best dose-fractionation prescription. Treatment personalization has been limited to date and focuses on mainly physical factors that constrain the possible dose distribution. However, genuinely personalizing a course of radiotherapy for any patient ultimately depends on integrating the physical aspects of treatment planning with quantitative models of predicted disease control and normal tissue complication risk. Tumors vary enormously concerning genomic alterations, vascular supply, cell density, transcriptomic profiles, hypoxia, glucose consumption, cellular radiation repair capacity, heterogeneity, and many other factors.[1] Invasion into surrounding tissues is also a highly variable process.[2–4] In addition, local control may depend on multiple host factors, including immune-related variables, such as tumor invasive lymphocytes (TILS).[5,6] Hence, individual tumors can be said to have individual dose-response curves that are steeper than population dose-response curves.[7] As discussed below, multidimensional information could further define cancer subtypes with steeper dose-response characteristics compared to the population average.

Figure 1 shows an example of dose-response curves for tumor control probability (TCP) and multiple toxicity endpoints, estimated for an early-stage non-small lung cancer treatment plan delivered at MSK.[8–10] Most of these curves are relatively shallow, making a truly

Address reprint requests to Joseph O. Deasy, PhD, Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY. deasyj@mskcc.org.

personalized optimization of radiotherapy for this patient difficult. Nonetheless, there are many reasons to believe that predictions willl improve. Cancer imaging relevant to radiotherapy response has become multimodal and quantitative and can be deployed during a course of RT. In-room imaging technologies and AI autosegmentation tools allow us to image and adapt radiotherapy routinely. The ability to sample or image many disease characteristics, including how they may change over the course of radiotherapy,[11] and to integrate all this information, together with biological predictors, into dose-response prediction models, promises a new era of clinical and research progress in radiotherapy. The challenge is to answer how all this information should be integrated into dose-response and physical-response (e.g., tumor regression) predictions. Which data elements or features are predictive, nonredundant, and practical to collect and routinely analyze? What is the optimal data integration and prediction method: through statistical models such as nomograms, comprehensive AI models, or minimal-complexity mechanistic mathematical models?

The need to accelerate efforts to model cancer and cancer treatments mathematically is now well-recognized. In a recent (2021) NIH-DOE series of workshops on advancing computational approaches for predictive oncology in the clinical and research domains of radiation oncology,[12] one key question identified was "How can we develop computational models to simulate how radiation kills a cell, affects a group of cells, transforms a tumor, and impacts a patient— and how does underlying patient-specific heterogeneity affect this process at multiple scales?" An important conclusion of the workshop was that patient-specific computer simulation "…provides a paradigm shift in oncology because it will enable data-driven simulation models to be integrated into routine clinical care—a key step toward the goals of precision oncology: to uniquely and continuously tailor treatment to each patient over time."

We are entering an era where new or improved informatics tools and analysis methods allow us to use many rich data sources within reach to better guide cancer research and treatments. Models of individualized disease response and normal tissue toxicity dose-response curves could be integrated directly into the planning optimization process.[13] New deep-learning tools in development will be able to track and monitor accumulated doses[14–17] and even predict tumor regression patterns over the course of treatment,[18] providing an improved basis for decision-making and plan adaptations. In this article, we briefly review a selection of information sources and model-building approaches for physically and biologically optimized radiotherapy. These include new opportunities based on real-world data, multidimensional imaging, radiomics and deep learning analyses, tumor and normal tissue genomics, monitoring longitudinal tumor changes, normal tissue complication modeling, and tumor control modeling. We emphasize the opportunities to advance radiation oncology via data science approaches, but this is not to diminish the critical role of hypothesis-driven preclinical studies and prospective clinical trials. Some important topics of relevance to data science, including blood based assays of tumor cells or circulating tumor DNA,[19] are only mentioned briefly.

Missing Real World Data (RWD) in radiation oncology.

Predictive model building typically starts with retrospective institutional datasets. However, the lack of well-annotated real-world datasets is a major obstacle to advancement in radiation oncology.[20] While data on patient characteristics, imaging, pathology, genomics, and treatments can theoretically be integrated, this is rarely done in practice and is not well-supported by current informatics systems. Our experience is that the reliability (i.e., correctness) of data collected during clinical workflows correlates with clinical usefulness.[21,22] This is yet another incentive to develop more effective clinical workflow tools in radiation oncology, a win-win proposition.[23]

New informatics tools and AI large language models (LLMs) could help create more complete "patient data stories" by automatically and reliably extracting information from unstructured health record narratives, inferring context, and linking data elements.[24–30] This could increase RWD's availability to improve research and clinical care.[31,32] Data standards, shared ontologies, and increasingly standardized electronic health record systems support the feasibility of large-scale RWD datasets.[33,34] Patient data stories can be made comparable and computable using graphs.[35] Graph-based analyses could probe numerous real-world issues, such as differences in outcomes reported between different classes of healthcare systems[36] or possibly the impact of an initially incorrect cancer diagnosis. However, fully representing the patient story computationally, even for the application of clinical guidelines,[37] is an unsolved problem. The scale and presence of errors in clinical datasets also represents methodological obstacles. Using a new generation of AI tools to monitor narrative dictation in real time to flag ambiguities or to identify missing data elements could increase the efficiency and reliability of RWD collection. For clinical data mining, an "hypothesis laundering" approach could leverage machine learning on large "dirty" RWD datasets to generate a relevant hypothesis, which could then be rigorously tested on a smaller, curated "clean" dataset. This would balance the benefits of analyzing large datasets with the need for rigorous hypothesis testing. Creating comprehensive, integrated RWD datasets and computable patient stories has implications beyond specific medical fields and could potentially improve the applicability of medical guidelines and algorithms more broadly. Capturing comprehensive clinical data that is structured and computable could enable a new era of true learning health systems.[20]

Connecting radiobiology and genomics.

Tumor and germline genomics have shown significant potential for improving patient-specific dose-response predictions. Torres-Roca and colleagues developed the Radiosensitivity Index (RSI) based on tumor mRNA expression profiles for 10 key genes and demonstrated impressive predictive power for local control and survival endpoints across multiple cancer types.[38–42] This has been further refined into the genomically adjusted radiation dose (GARD) metric by Scott et al.[43] These results firmly establish the relevance of gene expression patterns in determining clinical radiation response. Increasingly comprehensive multi-omic screens of radiosensitivity have recently become available.[44] Manem and colleagues have recently developed multigene mRNA radiosensitivity predictors using multiple preclinical datasets.[45,46]

The genomics of normal tissue radiation response (often called radiogenomics) is also a promising target for continued progress. Single gene validation studies have generally not been positive, probably because effect sizes from individual alleles are typically small,[47] although the XRCC1 single-nucleotide polymorphism (SNP) appears to be important.[48] Efforts to build multigene predictive models by the REQUITE genome-wide association studies (GWAS) consortium have shown promising performance for multiple endpoints.[49,50] In addition, several recent studies have shown that machine-learning approaches applied to germline GWAS can classify toxicity risk based on multi-SNP models.[51–55] In particular, the novel preconditioned random forest regression (PRFR) algorithm developed by Jung Hun Oh and colleagues[54] has successfully predicted risks for multiple postradiotherapy endpoints, including late rectal bleeding,[54] erectile dysfunction,[54] urinary toxicity,[56] hematuria,[52] and radiation-induced second breast cancers.[57] Post-hoc network analyses of the models can identify relevant interacting genes and biological pathways contributing to toxicity risk. For normal tissue toxicity, tissue-specific genes and pathways involved in maintenance or function are often identified as important, rather than DNA damage repair pathways. The REQUITE consortium has also shown that an AI sparse autoencoder approach is effective for multi-SNP toxicity prediction.[58] These results together indicate the potential of machine learning and AI methods applied to GWAS to produce genomic profile risk models predictive enough for clinical use. A critical future obstacle will be making this area of research beneficial to all patients, not just those in the largest ethnic and racial groups.[59] The decreasing cost of obtaining patient germline profiles makes this approach feasible for clinical implementation. However, continued multi-institutional collaborations will be required to produce clinically useful and validated tools.

Quantitative imaging biomarkers can help refine patient-specific dose-response curves.

Many baseline imaging parameters are relevant to radiotherapy response.[60–62] Quantitative imaging has shown significant potential in predicting and assessing radiotherapy response through various biomarkers and techniques.[63] We mention a few salient results: FDG-PET imaging predictors often correlate with poor outcomes. For example, higher SUVmax values correlate with more aggressive disease and radioresistance in head and neck cancers and NSCLC.[64] A modeling analysis of published data for oropharyngeal cancer estimated that tumors with abovemedian SUVmax values required about 20% higher radiation dose to achieve the same local control rates as those patients with below-median values.[62] MRI apparent diffusion coefficient (ADC) imaging has been shown to correlate with local control for multiple tumor sites.[65–67] Lower diffusion relates to greater cellular density and worse local control.[68] Pretreatment hypoxia, imaged, for example, using PET F18-labeled misonidazole (F-MISO)[69,70] has been correlated with poor outcomes in many tumor sites.[71] Hypoxia has also been associated with an immune-cold microenvironment in colorectal tumors.[72] It should be emphasized that all these methods of interrogating the tumor are closely linked. Figure 2 illustrates this by relating image-based metrics extracted for an H&N cancer cohort.[73] Closely correlated metrics are directly connected in the graph. It may be surprising to see a strong correlation between, for example, MRI-ADC values and PET-FDG mean standard uptake values in the lesion. Understanding these correlations

could be a key to defining actionable yet practical clinical biomarkers. Quantitative imaging measures of residual disease may also be coupled with serum molecular measures of disease under development.[74,75]

Extracting more information from images: radiomics.

Extracting more detailed imaging features, called 'radiomics,' provides potentially useful inputs for predictive models.[76–78] Recent reviews summarize evidence that radiomic models can provide histopathological and prognostically relevant information for many disease sites and subtypes.[79–93] Radiomic features could be tested for inclusion in patient-specific dose-response models. For H&N tumors, Mukherjee et al.[94] showed that radiomics models can predict tumor grade, perineural invasion, lymphovascular invasion, extracapsular spread, and HPV status. van Dijk et al.[95] recently reported on an internally- and externally-validated model that used CT features and machine learning to identify H&N cancer classes of widely varying local control and overall survival levels. In some cases, the multi-modal bivariate distributions of image features may be important, as shown by Vallières et al.[96] in predicting metastatic spread from sarcoma tumors using co-located FDG-PET and MRI features. Important problems still persist with radiomics methods, however, including understanding the inter-relationship of unusual features with more standard prognostic metrics such as tumor volume.[97]

Predicting tumor phenotypes with deep learning.

More recently, artificial intelligence (AI) methods have often been used to further probe the predictive value of image characteristics.[98,99] Deep learning AI image analysis tools essentially start with simple features and build up many combined features of different characteristics and scales.[100] The learning process emphasizes features meaningful to the selected learning task, which may be an outcome endpoint. A recent review concluded that deep-learning-based models outperformed radiomic feature modeling in 65% of reported comparisons.[101] However, low-dimensional radiomic models are more explainable, and understanding what key imaging features drive classification in individual cases may be critical to clinical adoption and to advancing cancer science.

Computer science advances in algorithms and techniques are being rapidly translated into medical imaging applications, and in particular, the impact of deep learning models on predicting outcomes based on clinical images is accelerating. For example, the recent publication of De Blase et al.[102] showed that multiple standard clinical images could be combined, in this case including CT and FDG-PET images, as well as gross disease planning contours, within deep learning frameworks to predict multiple endpoints, including the risk of local failure and distant progression. Ma et al.[103] in work from the same group, showed that a hybrid CNN vision transformer architecture could be used to develop a robust model to predict multiple endpoints, including local failure, distant progression, and overall survival. Patients in the low-risk groups (about 40%) for local-regional control and distant progression had few events during followup. HPV status was captured and accounted for separately from the deep learning predictions in the final prediction.

Another recent approach to using deep learning was published by Jiang et al.,[104] who showed that multitask learning for gastric cancers could improve both performance and the interpretability of deep learning predictive models. Learned endpoints included the response to chemotherapy and immunotherapy and the tumor microenvironment. Significant splits in survival curve predictions may reflect distinct biology or radiobiology. It should be emphasized that validated image classification signatures could be applied to scans for surgical patients and correlated with underlying genomic and pathological signatures from surgical specimens to identify cancer subtypes. The correlation of tumor genomics with radiological phenotype is often called 'radiogenomics,' which is often confused with using the same term to mean radiosensitivity genomics. Shui et al. recently reviewed the substantial progress in relating specific radiomic features to clinically meaningful genetic tumor subtypes.[105] Qian et al.[106] have recently reviewed efforts to correlate lung cancer radiomics with underlying genetic or pathology markers. Deep learning approaches for cancer subtype classification and survival prediction using radiological imaging data show promise for providing biological insights, even without full integration with genomic data.[107] For example, a study on lung adenocarcinoma patients used deep learning and radiomics networks based on CT imaging to predict histologic subtypes.[108] The ability to predict outcomes from imaging alone could potentially guide treatment decisions and provide prognostic information noninvasively. Even without full data integration, deep learning overall survival classifications could be compared with genomic processing of tumor surgical specimens (mRNA, methylomics, copy number variations, spatial transcriptomics, etc.), potentially extending the ability of imaging to 'see biology.' The noninvasive nature of imaging could allow for longitudinal monitoring of tumor evolution and treatment response in ways not possible with tissue sampling.

While radiomic and deep learning quantitative imaging correlates show promise, challenges remain in harmonizing data across different scanners and protocols to reduce bias and improve clinical applicability.[109] Ongoing research aims to overcome these obstacles and enable the widespread use of quantitative imaging in predicting and assessing radiotherapy response.

Capturing the longitudinal phenotypes of cancer.

The concept of a temporal disease trajectory in cancer and the potential for improved tracking of tumor growth rates represents a significant opportunity in oncology. We use the term temporal disease trajectory to refer to the progression of cancer over time, including its initiation, growth, response to treatment, and potential recurrence. Understanding this temporal and spatial trajectory is likely helpful for several reasons. In particular, a better understanding of the disease trajectory can help predict patient outcomes and adjust treatment strategies accordingly. The rate of growth can be an indicator of tumor aggressiveness, helping to guide treatment intensity. Studying temporal trajectories across many patients can reveal new insights into cancer biology, such as subtype and treatment efficacy. New streams of temporal information are also critical to leveraging the "digital twin" approach to guiding cancer care.[110,111]

Monitoring tumor growth rates before, during, and after treatment would be a paradigm-shifting practice that offers many benefits. This could provide a rapid assessment of whether a chosen therapy is effective, allowing real-time adaptations to treatment plans based on tumor response and possibly identifying the development of treatment resistance before it becomes clinically apparent. Detailed growth rate data can also drive new biological investigations, for example, by correlating growth rates with genomic data to identify key drivers of tumor progression and exploring how the tumor microenvironment (e.g., hypoxia, cellular density) influences growth rates and treatment response. As one example, Attalah et al. reported that the growth rate of lung tumors before RT is a strong negative predictor of both local control and overall survival.[112] They later validated this finding in a separate cohort.[113] They concluded that "SGR [tumor specific growth rate] can be used in conjunction with other well-known predictive factors to formulate a practical predictive model to identify subgroups of the patient at higher risk of recurrence after SBRT."

Changes in imaging parameters during radiotherapy have also been shown to correlate with outcomes. For example, for nonsmall cell lung cancer (NSCLC) patients, a more substantial reduction in SUVmax observed over the course of radiotherapy correlated with better outcomes.[114] As discussed further below, the resolution of PET-detected hypoxia early in treatment is associated with better outcomes.[115] Intratreatment changes in MRI apparent diffusion coefficient (ADC) values, related to tumor cell density, also predict outcomes.[66,116] Trada et al. have shown that, in head and neck cancer, a combination of increasing ADC and decreasing FDG-PET metabolic tumor volume correlates with treatment success.[117] Intratreatment changes in cfDNA may also help guide adaptations.[118] For NSCLC patients treated with stereotactic body radiotherapy, Residual FDG-PET at 12 weeks post-RT is well-correlated with local failure.[119]

Changes in imaging features during therapy, often called delta-radiomics, have been extracted to predict response. Delta-radiomics features have been shown to be predictive in multiple settings, beyond baseline values, for example: H&N local progression 3 months post-RT based on cone-beam CTs,[120] local control for NSCLC based on weekly CTs,[121] pancreatic cancer pathological response based on per-fraction CTs,[122] and NSCLC response to immunotherapy post-RT using contrast CTs taken after 2 to 4 treatment cycles.[123] Regarding normal tissue toxicity, in RT for H&N cancer, weekly CT delta-radiomics have also been used by van Dijk et al. to improve the early prediction of xerostomia.[124] Thor et al. showed that early expansion of the esophagus during RT for NSCLC as determined on weekly MRIs was correlated with the later development of severe acute esophagitis.[125]

Longitudinal tracking of metastases.

For patients who develop metastases, quantifying the time course could be impactful. For example, Hsu et al.[126,127] recently developed a deep learning methodology and software system for automatically tracking the appearance and location of brain metastases across multiple longitudinal MRI scans. Patients vary widely in terms of temporal and spatial patterns in the appearance of brain metastases, e.g., widespread metastases appearing a few months after treatment vs. an isolated metastasis appearing years later. Understanding how such factors should guide treatment management requires routine quantitative tracking

in space and time. Tracking brain metastases' temporal/spatial appearance and correlating with underlying primary and metastatic biology may lead to valuable scientific and clinical insights. AI tools for monitoring the volume change of tumors can be more reliable than by-eye RECIST size marking.[128] New and future AI methods will likely be able to track tumor changes in detail, even giving information about how a tumor grows or loses mass and the variability of mass density changes across the tumor volume. Patient-specific histograms of tumor mass gains or losses per unit time could provide a new window into disease prognosis and treatment response.

Data integration challenges.

Standard nomograms typically use regression modeling to combine quantified risk levels from multiple data elements. However, the high-dimensional information in genomics, radiological imaging, and pathology features must arguably be related. Hence, more effective integration of multiple data types requires building topological cross-links that are currently primarily unknown. For several reasons, multimodal data integration in oncology offers significant potential for improving research, diagnosis, and clinical management. Different diagnostic modalities provide complementary insights that are crucial for comprehensive treatment management. For example, integrating imaging, histopathology, genomics, and clinical data can offer a more complete picture of a patient's condition than any single modality alone.[129,130] Combining data from multiple modalities can potentially increase the accuracy of prognostic models. Integrated analyses can potentially reveal overlaps or shared dependencies between different data types, providing a deeper understanding of disease mechanisms and patient outcomes.[130] Multimodal data integration may be more effective at identifying important cancer subtypes or host interactions that are not apparent when examining single data types in isolation.[131] In addition to graph-based integration methods, AI-driven data fusion strategies include early fusion (combining raw data or features at the input level), late fusion (aggregating predictions from separate unimodal models), and intermediate fusion (iteratively learning improved feature representations under a multimodal context).[130] Disparate systems of different kinds and scales must be integrated for optimal predictive power. Consequently, multiscale modeling coupled with machine learning is also an important data integration and modeling methodology.[132,133]

AI methods can be used to convert one type of data into another type (imperfectly), potentially establishing important co-dependencies. For example, a deep learning model can use standard pathology slides to estimate molecular marker densities usually only available with more advanced immunofluorescence methods.[134] The problem of integrating high dimensional data of multiple data types into a joint network is an active area of investigation. Jaume et al.[135] presented a transformer model (named SurvPath) that can learn the relationships between whole slide pathology features and bulk transcriptomics. Outside of AI, high-dimensional biomedical data is typically represented in a connected graph format, with links indicating a strong correlation or known chemical reactions. Some networks can be built from known interactions (such as protein interaction networks), whereas network topologies for other data types need to be constructed, for example for radiomic features. This can be done, for example, by analyzing the correlations of radiomic

features derived from relevant image collections.[136] A subject sample can be represented as a normalized distribution in such a network. Optimal mass transport theory is a powerful method for quantifying the closeness of any two samples. Multiple data types can be represented as multigraphs with some inter-modality cross-links. Using such methods, meaningful comparisons can be made on high-dimensional spaces with a modest number of subject samples. As an example of multimodal non-AI data fusion, Pouryahya et al.[131] integrated breast cancer multiomics (mRNA, copy number variations, and methylomics) on a graph network representing known gene interactions. Unsupervised optimal mass transport distances were used to cluster distinct subtypes, resulting in identifying a biologically distinct and particularly lethal subtype.

The heart of radiotherapy is the tissue-registered dose distribution. Hence, developing improved Normal Tissue Complication Probability (NTCP) models is crucial for advancing radiotherapy treatment planning and optimizing patient outcomes. One key is assembling appropriately large multi-institutional datasets. In addition to the QUANTEC papers,[137] which are now more than a decade old, many of the important issues are discussed in the comprehensive book edited by Rancati and Fiorino.[138] Despite extensive research into NTCP models, clinical practice still heavily relies on dose-volume threshold constraints. While these constraints are practical, they greatly oversimplify the complex relationship between the dose distribution and tissue response. Validated NTCP models have the potential to provide more nuanced and relevant information about treatment outcomes compared to standard dose-volume constraint guidelines.[139,140] As noted above, many NTCP risk curves are relatively shallow, meaning that complications risk changes gradually with dose. Converting these curves into binary dose-volume constraints can lead to overemphasizing specific thresholds and losing important context about the continuous nature of risk.[137]

A significant challenge in developing robust NTCP models is the limited variance in dose-distribution data from institutions that adhere to consistent dose-volume constraints. This lack of variability in potentially predictive dose-volume metrics makes it difficult to derive comprehensive NTCP models that accurately reflect the full range of the dose-response relationship. Unsurprisingly, NTCP models that combine multi-institutional and multiprotocol data can demonstrate altered tolerance relationships[141]. There is an opportunity to create multi-institutional treatment plan dose-distribution databases, which could provide a broader range of dose-distribution data, allowing for the development of more robust and generalizable NTCP models.

While privacy issues are an obstacle for multi-institutional databases, advanced techniques for mapping dose-distributions to representative patient anatomies offer a potential solution. Point-wise correlations with outcomes, called 'voxel based analysis,' can provide essential insights into toxicity predictors.[142–146] These methods could allow institutions to contribute anonymized dose-distribution data while maintaining patient privacy.

Most NTCP model building is low-dimensional, using only a few fitting parameters to conserve statistical power. One effective method for building low-dimensional and interpretable dose volume predictive models is to use ensemble model methods, for

example, by combining ('bagging') models constructed on bootstrap data replicates. Thor et al.[147] used this approach to effectively model the overall survival impact of irradiating cardiopulmonary structures in the RTOG 0617 clinical trial data.

Spatial NTCP models aim to geometrically represent the 3D dose distribution, allowing for a more comprehensive analysis of dose patterns and their impact on normal tissue complications.[148] Analogous to genomics and radiomics, 'dosiomics' is a term used to describe the more general extraction and modeling of dose features to predict outcomes.[149] Multiple recent efforts have been made to improve toxicity predictions using deep learning based primarily on the dose distribution.[150] Men et al.[151] used a deep learning approach to predict xerostomia following H&N RT based on the dose distributions of RTOG trial 0522. Humbert-Vidan et al.[152] recently reported that deep learning could beat a random forest approach for predicting mandibular osteoradionecrosis. Reber et al.[153] recently investigated machine learning and deep learning approaches to predicting osteoradionecrosis from dose-distribution data. Machine learning on extracted features had superior performance compared to deep learning. Other work has demonstrated that deep learning can be useful in classifying the risk of xerostomia in head and neck treatment plans[151].

A recent exciting trend is the combination of tissue image features, whether extracted by radiomics or deep learning, with dose distribution features to predict toxicity risk. El Naqa et al.[154] recently showed in a pioneering deep learning analysis that liver MRI images could be used to classify liver function and feed into a more traditional NTCP model of liver toxicity that accounts for dose-volume characteristics. Bin et al.[155] used lung ventilation images in addition to the dose distributions as inputs to deep learning to improve the prediction of post-RT pneumonitis. An exciting aspect of their study was that they weighted the dose distribution by estimated ventilation values to create 'functional dose' maps. Zhang et al.[156] recently constructed a nomogram that combined a lung radiomics score with a dosiomics score and other clinical variables to predict pneumonitis.

Predicting the tumor dose-response curve.

Tumor Control Probability (TCP) modeling has evolved significantly to incorporate more realistic and mechanistic factors that impact tumor response to radiation therapy. We do not consider radiopharmaceutical therapy here, which has a set of distinct issues.[157] As noted above, many TCP curves are relatively shallow (changes of 1–2% absolute increase in TCP per 1% increase in dose are typical.[158]) This shallowness is presumably due to a mix of previously unquantified factors that impact response. The mathematical goal of TCP modeling is to produce models that agree with clinical data and have steep dose-response curves. The scientific goal is to create models with a valid mechanistic basis so they can be extrapolated beyond the current data, even if just hypothetically. Here, we summarize some key factors in TCP modeling. The cellular access to oxygen or lack thereof (hypoxia) is nonuniform on both the microscale and the macroscale in human tumors.[159,160] Hypoxia is known to correlate with poor clinical outcomes, as noted above.[161] Incorporating hypoxia into TCP modeling is critical because hypoxic tumor cells are more radioresistant[162,163] and also because hypoxia negatively affects other important factors, particularly reducing cellular proliferation.[164,165] Not all tumor cells are stem cells

capable of regrowing a tumor. Variation in stem cell fraction is also important and likely impacts the dose needed for control, similar to what is shown in preclinical studies.[166] This is not currently accounted for in human TCP models,[166] although spatial variability of tumor stem cell density could be taken into account.[167,168] Tumors are also known to be heterogenous in clonal lineage. Cellular radiosensitivity measured using in vitro cell survival experiments based on repeat biopsy samples has demonstrated very high variability (coefficients of variation of 30–40% being typical[169]). Early bioeffect models sought to compare values of "biologically equivalent dose" (BED), rather than predicting the resulting TCP directly. This was done primarily using the Poisson distribution, based on in vitro experiments, to calculate the probability of zero clonogens surviving after radiotherapy. Models further incorporated the linear-quadratic (LQ) cell survival model, which accounts for both single-particle-track DNA lethal damage (linear in fraction dose) and multiple-track lethal interactions (quadratic in fraction dose). Cellular proliferation itself is also a vital resistance mechanism, as mentioned above. Proliferation can increase during a course of RT due to cell death and decreased resource competition, mimicking a reversal of Gompertzian (i.e., slowing) growth curves. This can reduce overall treatment efficacy, especially for longer treatment courses.[170] For this reason, a time factor has often been added to the LQ framework to reflect a reduction in local control for treatments of increasing overall treatment time past an assumed 'kickoff time.'[171] This applies for tumors that proliferate significantly during conventionally fractionated radiotherapy (i.e., most tumors, excluding very indolent tumors such as prostate).[171] The LQ model of tumor control has been used to analyze many radiotherapy datasets,[172–174] and has been extended, for example, to account for the kinetics of repair processes.[175]

Going beyond these simple bioeffect equations, some models attempt a more mechanistic approach. One critical test of any mechanistic TCP model is whether it can recapitulate clinical dose-response relationships with reasonable parameters. Unfortunately, validating biological mechanisms is almost always a challenge due to a lack of adequate test data. As one potential approach to capturing the dynamic response to radiotherapy, Jeong et al. have published a flexible tumor radiobiological simulation model based on established radiobiological principles as well as the novel concept of an "energy budget," representing the fact that, in a tumor, the competition for locally available oxygen invariably limits the fraction of cells that can progress through the cell cycle.[176,177] The model recapitulates many critical aspects of known tumor biology and radiobiology, including doses required to achieve local control, tumor volume regression during RT, high cell loss factors, volume doubling times much longer than cell cycle times, and the increase in the dose required as overall treatment time increases past 3–4 weeks. The usefulness of the model was demonstrated in a fit to all published RT protocol results for early-stage non-small cell lung cancer[178] (see Figure 3). In a further test, the same model could fit all the early-stage NSCLC radiotherapy outcome data from the Japanese carbon ion beam therapy results.[179] As shown by Crispin-Ortuzar, the model is also consistent with previously reported image-based predictors of radiotherapy response.[180] It is an open question whether this level of tumor dynamics is always needed as opposed to approaches with simplified dynamics.[181] One interesting prediction of this mechanistic model is that radiotherapy may be more

effective if delivered in a 'primer shot' approach, by giving a single fraction of 5–8 Gy followed by a break, to allow tumor reoxygenation, of 10 days to 2 weeks.[182]

Shrinkage of NSCLC tumors during RT has been positively correlated with improved outcomes.[183,184] Future developments of this or other TCP models could incorporate patient-specific imaging (e.g., FDG-PET, FMISO-PET hypoxia imaging, DWI-MRI) at baseline and changes measured during treatment using cone-beam CT (CBCT) or other modalities.[185–187] Compartment modeling is just one possible approach.

A different approach to tumor response modeling emphasizes using partial differential equations to model the physical image of a tumor including the invasive edge.[2,186,188–190] This can be linked with image-based machine learning as well. This approach has been used to predict tumor response to radiotherapy, for example in brain and breast tumors.[191] An advantage of this approach is that it leverages the behavior of the tumor shape for learning.

TCP models could incorporate any number of features representing different characteristics of the problem.[188,192,193] The impact of an immune contribution to dose-response may be considerable. For example, recurrence risk following post-op radiotherapy in the SweBCG91RT trial was reduced when tumor samples contained tumor-infiltrating lymphocytes (TILs).[194] Immune 'hot' tumors could be identifiable partly through radiomics or deep learning models.[195,196] The best modeling approach depends on the clinical use case, the disease site, histology, and the treatment modality. Preclinical studies are also an underused potential source of modeling data.

Local control is undoubtedly also a function of dose to subclinical disease, which has been shown to have an exceptionally shallow dose response.[197] Unexplained failures to control early-stage NSCLC tumors, even at high doses, may be related to hard-to-image tumor cells in the peri-tumoral region, as indicated by the results of Davey's model.[198,199] In prostate cancer, the impact of daily kV image-guidance on outcomes has been shown to be related to the predicted likelihood of extracapsular extension.[200] Bortfeld and colleagues have recently been studying how the nonimageable component of disease could be modeled and probabilistically estimated.[201,202] Unkelbach and colleagues have been using models to estimate the probabilistic likelihood of lymph node spread in head and neck patients.[203]

The impact on TCP of low-dose regions inside or, more commonly, on the edge of a tumor is relatively unknown, although calculations can be made under assumptions.[197] The ICRU paradigm (updated in ICRU 83[204]) rather dogmatically assumes that the proper guidance in RT is not to allow any drop in the prescription dose near the edge of a tumor. In the presence of localization uncertainty, subclinical disease uncertainty, and unavoidable dose-rolloff, this 'paranoid target volume' approach implies that large margins of normal tissue must also be irradiated to high doses. This already seems at odds with the recognition that RT is a balance between disease eradication and normal tissue toxicity.[205,206] Fortunately, the stereotactic prescription approach that allows for more target volume dose heterogeneity and is more comfortable with dose gradients at the edge of a tumor seems to have superseded or at least supplemented the ICRU 83 guidance. Continuing improvements in pretreatment and on-table imaging also support this transition. The ICRU approach does not optimally manage

how localization uncertainties are handled.[207] A critical knowledge gap could be filled by inter-institutional analyses of the impact of target dose heterogeneity (e.g., GTV and PTV dose heterogeneity) on TCP. We hope these brief comments clarify that personalized TCP models could become much more refined and comprehensive while retaining scientific interpretability. Nonetheless, deep learning approaches directly on target dose distributions may lead to improvements in predictive power. For example, Dudas et al.[208] recently used deep learning to estimate the risk of local failure for NSCLC treatments. Analysis showed that the dose periphery was the most predictive region (see Fig. 4). This may be related to peri-tumoral sub-clinical extension, as predicted by Davey's model, discussed above.

In summary, there is an urgent need to identify tumor subtypes and other radio-response factors to provide steeper dose-response relationships to guide treatment planning and personalized prescriptions. Validated predictive models, although difficult to build and validate, could utilize widely available data sources to have a positive impact on the treatment process of millions of cancer patients worldwide. Advances in radiation oncology modeling could connect radiobiology with current themes in cancer biology, support the rational use of multimodality imaging and integration with genomics, and give clinicians much more precise and personalized insights into prescription and planning tradeoffs. Predicting and monitoring early tumor response to treatment, informed by digital twin tumor simulations, could guide adaptive tumor prescription changes. How much effort will be required to perform these studies, and what is the potential payoff? Figure 5 shows our speculative schematic summarizing many of the topics reviewed here, ordered by the estimated level of resources required along the x-axis and the estimated upper ceiling of potential significance along the y-axis. We invite you to mark up the image based on your own estimations of what efforts would be most impactful. While many studies may be pursued by single institutions, multi-institutional studies, and even cooperative group studies will typically be required for themes to reach their full translational significance. Many under-developed aspects of radiation oncology data science could drive simultaneous improvements in disease control, toxicity avoidance, and efficient patient management.

Acknowledgments

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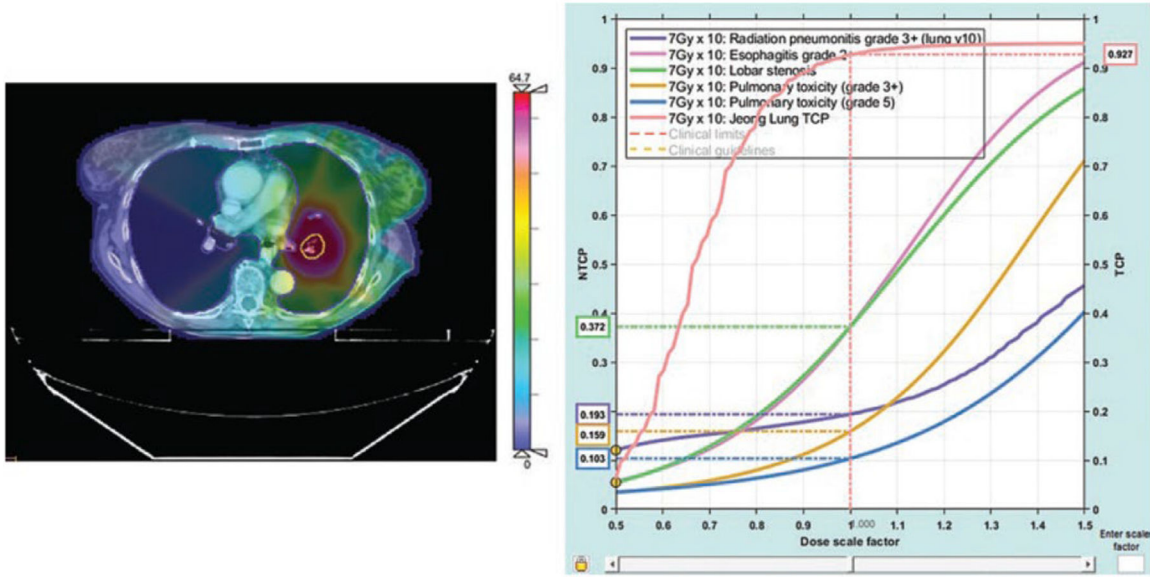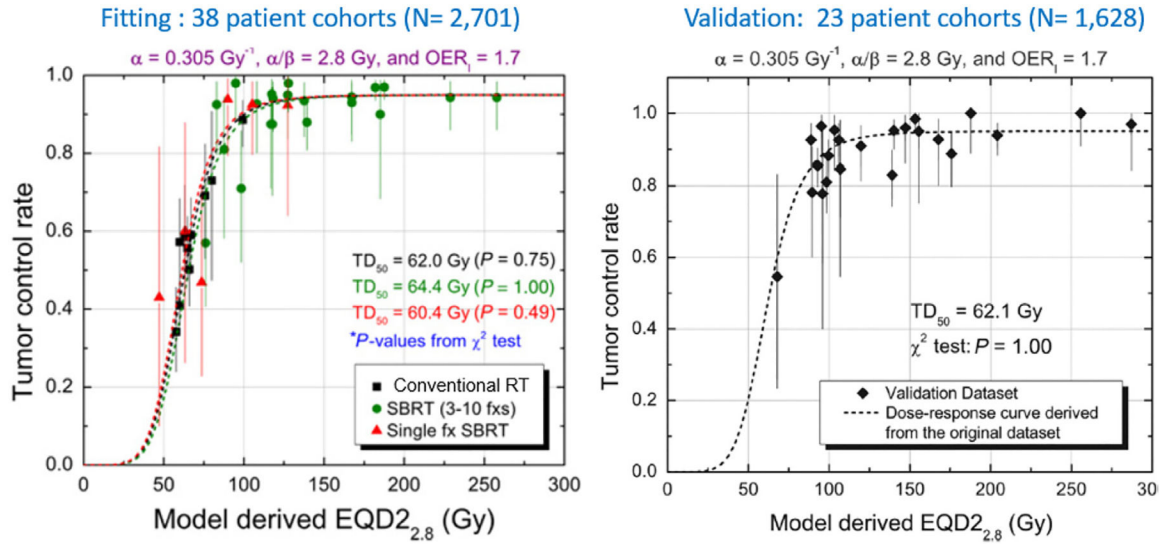
Figure 1.

Lung cancer radiotherapy patients have individualized dose-response curves. Dose-response predictions, for tumor eradication and normal tissue risks, calculated for an early-stage nonsmall lung cancer treatment plan. Left: A planning CT scan overlaid with a dose colorwash. Right: the left-most curve shows the probability of local control, which is high for this dose and fractionation prescription (93%). The risk of toxicities (pneumonitis, esophagitis, bronchial stenosis) are shown. All curves intersect a 1.0 scale factor at the prescription fraction size. Data science could drive the development of predictive models that account for underlying biology and radiobiology, providing an improved basis for treatment decisions [reprinted with permission from[10]]).
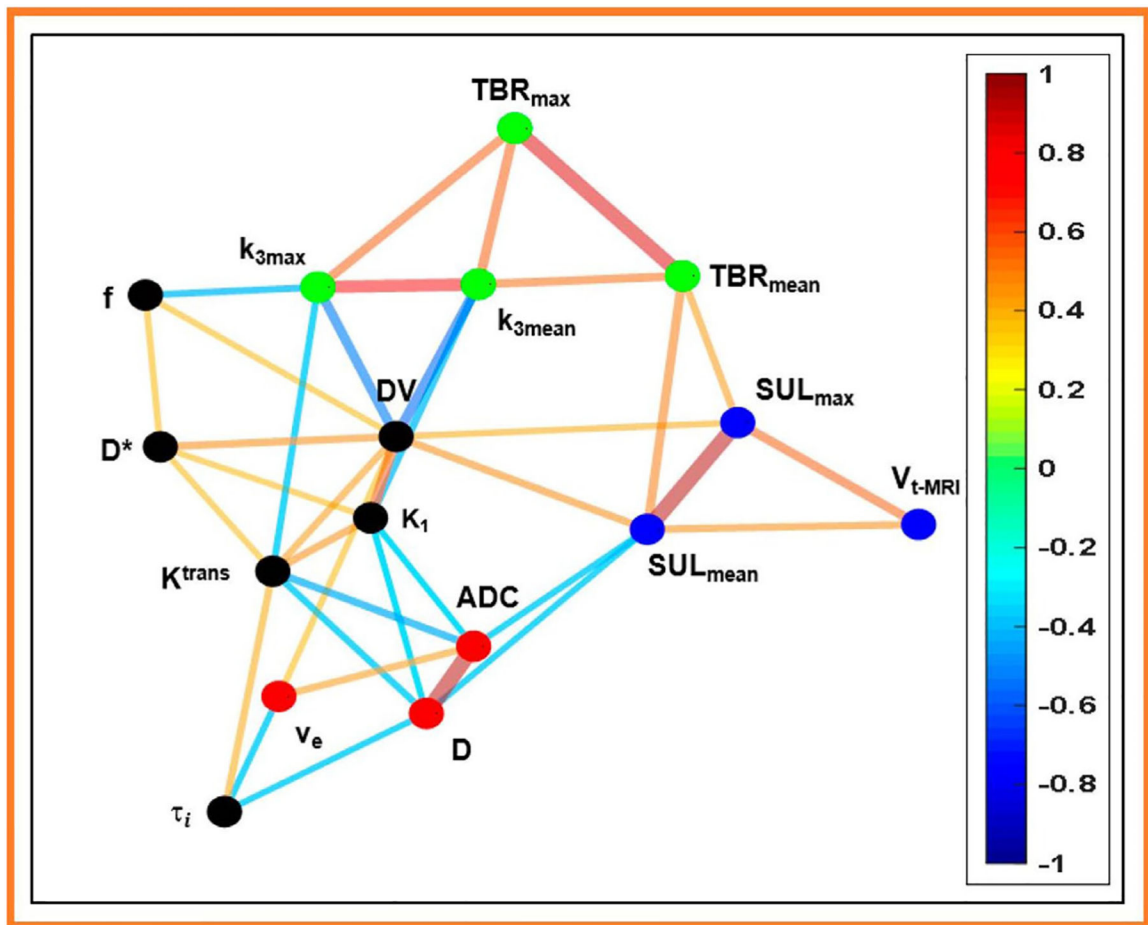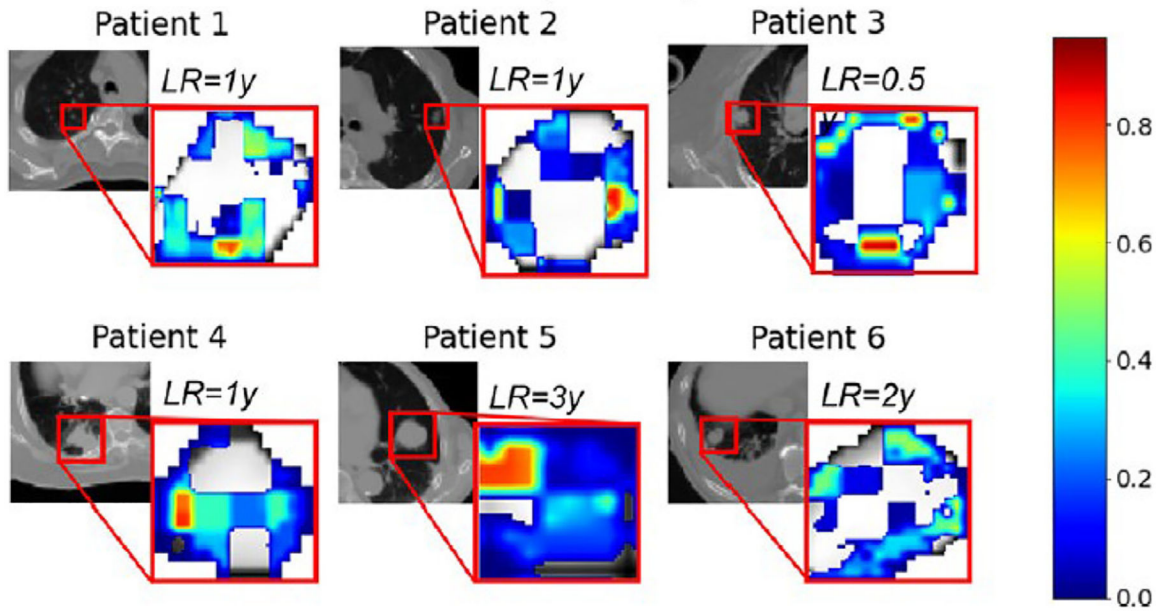
Figure 2.
A relatedness graph of quantitative metrics derived from images for H&N cancer patients (N=23), as reported by Paudyal et al.[73] Image types include FDG-PET/CT (SUL [lean body mass corrected SUV], FMSIO-PET/CT (K_1 [perfusion], k_3 [hypoxia], TBR [hypoxia tumor blood ratio], and DV [distribution volume]), DW-MRI (ADC [apparent diffusion coefficient]), IVIM (D [true diffusion coefficient], D^* [pseudo diffusion coefficient,] and f [perfusion fraction]), and FXR DCE-MRI (Ktrans [volume transfer constant], v_e [volume fraction of extravascular and extracellular space], and τ_i [intracellular water mean lifetime]). A spin-glass model was used to derive closely-related communities, indicated by node color. Edge color refers to Spearman's rank correlation coefficient, ρ. (Used with permission).
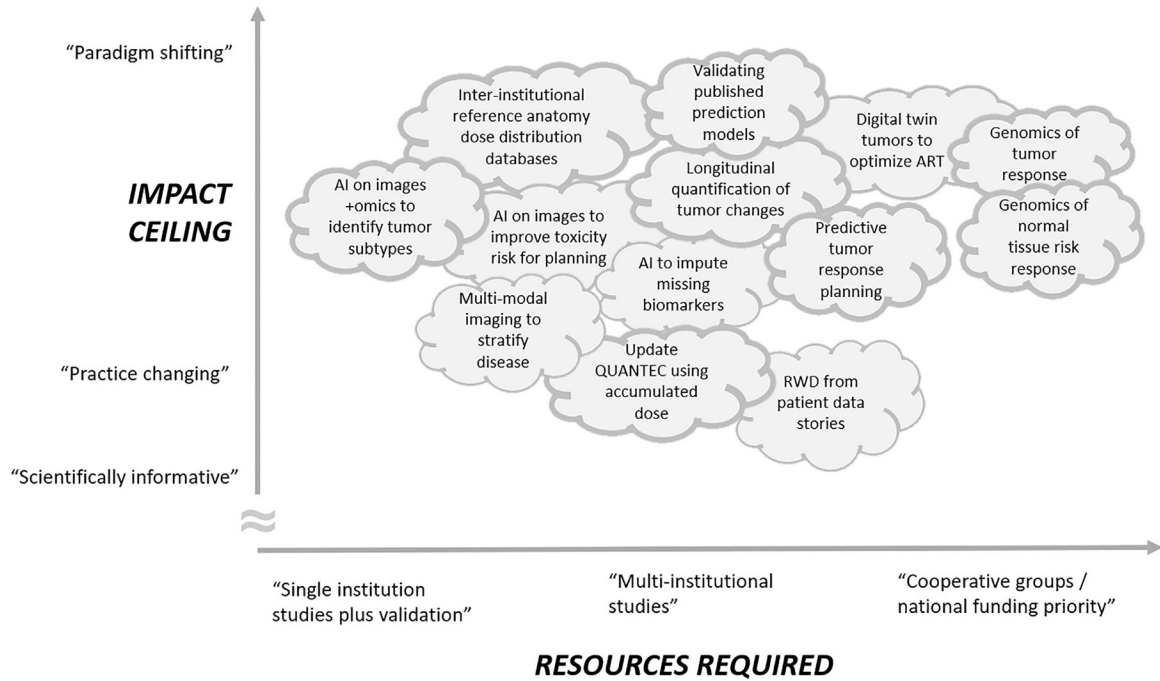
Figure 3.

The Jeong model fit to all analyzable Stage I (localized) NSCLC cohorts as reported in Jeong et al.[178] Left: 4-parameter model fit to 38 cohorts (published by 2010 and before, plus two internal datasets); Right: Validation test of fitted model to separate cohorts (published 2009–2014.) This mechanistic model is the first model of any kind shown to well-fit RT response across all fractionation regimes, from single fraction delivery to 2 Gy per weekday. The model identifies the point of dose intensity beyond which response flattens, regardless of fractionation (reprinted with permission.)

Figure 4.

In a deep learning model published by Dudas et al.[208] to predict the likelihood of local failure, attention analysis shows that the dose near the target volume edge was critical. (reprinted with permission.)

Figure 5.
To stimulate thinking, we estimate the payoff versus resources required for developing and implementing modeling approaches we have discussed. We invite the reader to 'correct' the diagram.