Artificial intelligence in radiation oncology treatment planning: a brief overview

Kendall J. Kiser[1,2,3], Clifton D. Fuller[1], Valerie K. Reed[1]

[1]Department of Radiation Oncology, the University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [2]The University of Texas Health Science Center School of Biomedical Informatics, Houston, TX, USA; [3]The John P. and Kathrine G. McGovern Medical School, Houston, TX, USA

Correspondence to: Kendall J. Kiser, BS. Department of Radiation Oncology, the University of Texas M.D. Anderson Cancer Center. 1515 Holcombe Blvd., Houston, TX 77030, USA. Email: Kendall.j.kiser@uth.tmc.edu.

Abstract: Among medical specialties, radiation oncology has long been an innovator and early adopter of therapeutic technologies. This specialty is now situated in prime position to be revolutionized by advances in artificial intelligence (AI), especially machine and deep learning. AI has been investigated by radiation oncologists and physicists in both general and niche radiotherapy planning tasks and has often demonstrated performance that is indistinguishable from human experts, while substantially shortening the time required to complete these tasks. We sought to review applications of AI to domains germane to radiation oncology, namely: image segmentation, treatment plan generation and optimization, normal tissue complication probability modeling, quality assurance (QA), and adaptive re-planning. We sought likewise to consider obstacles to AI adoption in the radiotherapy clinic, now primarily political, legal, and ethical rather than technical in nature.

Keywords: Artificial intelligence (AI); computer assisted radiotherapy; image guided radiotherapy; machine learning; radiation oncology

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Introduction

Cancer care delivery generally, and radiotherapy specifically, is highly dependent on integrating data from multiple sources. The detail provided by a single datum can radically change a cancer patient's management strategy; for example, tumor genetic constitution (1), immunohistologic markers (2), a patient's demographic profile (3), or radiographic attributes (4) can each radically alter a patient's treatment course and/or prognosis. Radiation oncology embraces this complex treatment calculus and has long sought to deliver proven and precise radiotherapy courses (5,6). The data-diverse, technology-intensive nature of radiation oncology places it in a unique position among medical specialties to be revolutionized by the "fourth industrial revolution," artificial intelligence (AI) (7,8). The goal of this review is to give a brief overview on the role of AI in radiation treatment planning and related applications. *Figure 1* organizes steps in the radiotherapy treatment process and provides example AI use cases for each of them, and augments similar extant literature on this topic, towards which the interested reader is heartily referred (8-13).

Terminology of AI, machine learning, and deep learning

At base, it is initially of utility to clarify the oft-conflated terms "artificial intelligence," "machine learning (ML)", and "deep learning (DL)". AI is the practice and theory of developing "machines that can think and act as intelligently as humans" (14). Early AI pioneers primarily built it by programming logic rules into machines; however, rule-based AI has largely been subsumed by ML AI, especially in healthcare (15,16). Rather than manually programmed logic rules, ML relies on manually curated data inputs to "learn" patterns, often patterns that humans cannot discern and therefore cannot explicitly program as a logic rule. ML

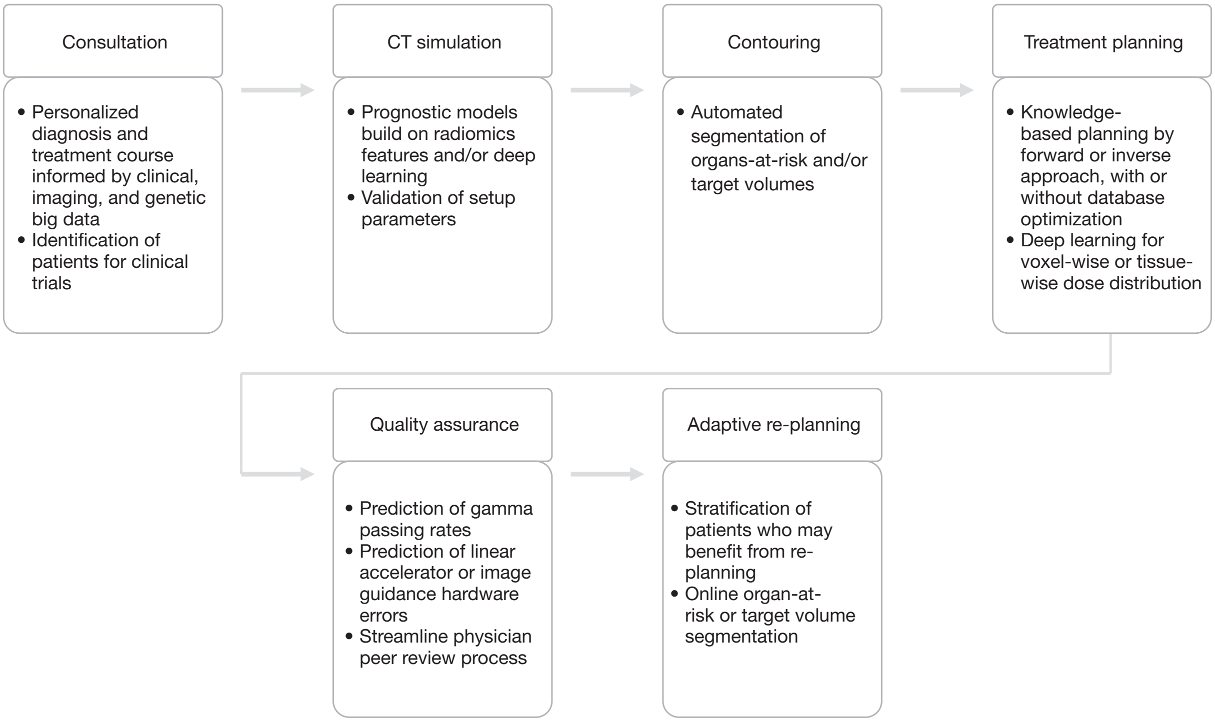

Figure 1 Applications of artificial intelligence to steps in radiotherapy planning and delivery. Selected examples of AI-driven contributions to radiotherapy planning have potential for reducing time, reducing inter-observer variability, and increasing accuracy in delivering radiation. These heavily scrutinized steps are data-rich and quantitative and thus naturally suited inputs to artificial intelligence algorithms. Not pictured in this figure nor deeply discussed in this paper are the considerable applications of artificial intelligence to cancer diagnosis, clinical trial patient recruitment, and post-treatment analysis of patient outcomes.

methods are based on advanced statistics and mathematics [a prominent ML book refers to it as statistical learning (17)] and there are many algorithms, each with strengths and limitations depending on the types and dimensionality of the input data. In turn, DL is a unique kind of ML that has yielded spectacular solutions to AI problems. DL architectures are inspired by the brain and facilitated by recent advances in computing speed and power and immense data stores for training the neural network architectures (16). DL differs from other ML approaches in that it can learn from "raw" data inputs rather than manually curated ones. The current hype surrounding AI is largely catalyzed by DL, which exploded into the public attention in 2012 (18). For further discussion of DL we refer the reader to reviews on the topic and to two *JAMA* viewpoints regarding its place in healthcare (15,16,19-22).

Auto segmentation

Manual segmentation (contouring) of target and normal structures is one of the most time-consuming aspects of radiation therapy and subject to significant intra and inter-observer variability. Therefore, autosegmentation algorithms have been developed to increase staff efficiency and improve consistency. Historically, the most commonly employed method for structure autosegmentation has been propagation of contours from an "atlas" or library of previously segmented images onto a new image by deformable registration (23,24). However, the accuracy of atlas-based methods suffers significantly whenever it encounters patients with unusual anatomy compared to their reference atlases (25), or by any contributor to tissue contrast variation. To circumvent this, more images can be added to the atlas to make it more robust, but additional images increase the computational load and decrease the method's speed.

DL, which to date has achieved broad success in image analysis and computer vision, appears to resolve the time and computation constraints inherent in traditional atlas-based methods. DL algorithms have been trained to segment cancer and organ-at-risk (OAR) structures in the head and neck (26-31), brain (32-34), abdomen (35,36), thorax (37-42), spinal cord (43), breast (44-46), and pelvis (47-50) at accuracies indistinguishable from human experts and with clinical workflow implementation and validation in some cases. Several studies have concluded that DL is more accurate than other algorithms with respect to the Dice Similarity Coefficient (DSC) (28,37,47,51,52), a standard volume-overlap evaluation metric used in segmentation literature (53). Segmentation methods based in deep learning are extraordinarily computationally demanding to instantiate, but once the model's hyperparameters and tensor weights are optimized, running it is computationally trivial and faster than atlas-based methods (26,54). For example, in the setting of lung cancer treatment Zhu *et al.* (55) directly compared DL and atlas-based OAR segmentations and found DL to output non-inferior or superior results for every OAR at faster intervals. This time advantage may be particularly significant in the setting of adapting the radiation plan while the patient is on the treatment table.

Nikolov *et al.* (27) is an innovative illustration of rapid, accurate DL-based target and OAR segmentation. The authors trained a 3D U-Net architecture end-to-end with 663 CT datasets acquired from their home institution and tested it independently on 24 multi-institutional datasets available from The Cancer Imaging Archive. In a novel step, the authors departed from the DSC evaluation metric in favor of an altered, "surface" DSC that more effectively penalizes segmentations that would require extra time to manually re-contour because of their surface area. The model segmented 19 of 21 OARs as well as expert English radiographers. The two exception OARs were the lens and brainstem. Lens segmentation has also been a challenge in other published work, but the performance of the algorithm on segmenting brainstem was explained by discordance in ground-truth segmentation labels regarding the definition of where the brainstem begins, leading to poor model segmentation at the brain-brainstem interface. This limitation notwithstanding, the model has potential to markedly hasten workflow with no compromise in segmentation quality.

Treatment planning and optimization

Our literature search suggests that radiotherapy treatment planning and optimization may be the single most popular ML/DL application in radiotherapy currently, suggesting physicists' faith in its potential for improving this task. In 19 of 45 Medline search results addressing radiation oncology and AI from January 2017 through January 2019, automated radiotherapy plan creation and optimization is the primary or secondary aim.

Radiotherapy plan optimization attempts to find the most satisfying solution to competing objectives: deliver the highest radiation dose to the target while delivering the least radiation to surrounding OARs, which are usually assigned a numeric weight to quantify their importance in the optimization calculus. This task requires physicists to iteratively fine-tune parameters that determine radiation dose deposition (usually modeled by Dose-volume histograms or DVHs) until a plan that meets the minimum acceptable threshold for each objective is generated. However, there is no guarantee that the first clinically acceptable plan is the most optimal one, and continued fine-tuning can continue indefinitely until time resources are exhausted and the planner is forced to settle on the best plan he or she could achieve.

Knowledge-based automated planning (KBP) methods have generated considerable attention in recent literature. KBP assists physicians and planners in obtaining the optimal OAR DVHs by employing ML methods that learn from databases of clinically acceptable plans. KBP uses geometric and dosimetric features from plans in the treatment library to predict a range of achievable DVHs for new patients. Obtaining this information early in the treatment process can assist in achieving the optimal treatment plan by forward planning. Alternatively, KBP model dose predictions can be used to directly generate plans by inverse optimization (56). KBP has been used to predict normal tissue DVHs in a variety of disease sites (57-61) and recently to predict which patients may benefit from proton radiation (62).

KBP methods have been commercialized in treatment planning systems (63-68). For example, RapidPlan™ (Varian Medical Systems, Palo Alto, CA) trains on past clinically acceptable plan DICOM files with beam geometry and the structure set on which the planner wishes to create objectives (per-structure minimum of 20 examples) to output an automatic plan with predicted DVHs for all objective OARs. RapidPlan™ can generate plans comparable to expert-generated plans (64,65) and superior to beginner and junior-generated plans (66). The RapidPlan™ ML algorithm details are proprietary but are inspired by Yuan *et al.* (69), who used stepwise multiple regression to learn anatomic and spatial image features that are germane to radiotherapy planning and then used principal component analysis to determine which of those features accounted for the greatest variance in OAR dose deposition.

As is the case for other applications of knowledge database-based automation, the cost of computation increases and speed decreases with increasing database size. The problem of computational inefficiency with large data inputs was intriguingly evaded by Liu *et al.* (70), who greatly downsampled the number of planning optimization ML algorithm inputs by first grouping voxels that were isodosimetric and spatially related using a *K* means clustering algorithm. Computational efficiency was markedly increased without sacrificing plan quality.

In aggregate, the literature to date strongly supports the feasibility of KBP automation and outlines possible next steps. Some have suggested that automation methods be trained with true patient outcome data rather than DVH tissue damage proxies (11). Wall *et al.* (71) hypothesized that if KBP knowledge databases for prostate cancer planning consisted of Pareto-optimized plans rather than merely clinically passable plans, the quality of the DVH predictions would significantly improve. A plan is Pareto-optimized if its competing objectives have been set such that an attempt to improve one objective compromises a hard stop for any other objective. Pareto-trained KBP generated plans showed significant improvement compared to plans generated by KBP alone. When past plans were re-planned using the Pareto-trained KBP the average decreases in dose to the rectum and bladder were respectively 9.4 and 7.8 Gy, while maintaining target dose.

In addition to KBP, DL has been investigated as a mechanism for automated plan generation (72-75). Fan *et al.* (73) and Chen *et al.* (74) independently undertook the similar task to predict dose distribution with a ResNet DL architecture. Although they trained their models on input data of different types and quantities, both groups demonstrated feasible DL-based automated plans that were similar to expert plans. Cardenas *et al.* trained a DL auto-encoder to delineate CTV contours that needed little or no manual correction (72). To capture CTV information, they used computed distances between tumor volumes and surrounding OARs as inputs rather than images. This work contributed the first automated clinically usable CTVs and a novel probability threshold function based on the DSC.

To our knowledge, no study has yet compared plan quality between DL and KBP or other automated methods.

Tumor control probability and normal tissue complication probability

Radiomics is an emerging field that extracts textural, morphologic, and intensity quantitative features from images when may then be used as feature inputs to ML algorithms. Radiomics features are a promising additional data type for oncologic outcome prediction and tumor control probability models (76). Multiple manuscripts have been published using radiomics to predict radiation response, in some cases with prediction power outperforming standard clinical variables (77-82), though not in all (83). Radiomics-based statistical approaches can predict various radiation normal tissue complication probabilities including radiation pneumonitis, xerostomia, and rectal wall toxicity (84-89). Radiomics data, coupled with genomic data and increasingly computable clinical record data, may escort radiation oncology into a new epoch of truly personalized radiation plans based on patient-specific knowledge.

However, important challenges surrounding standardization and reproducibility of radiomics-based predictors exist. For example, radiomics studies suffer from lack of standardization at multiple stages of image acquisition and processing. There is currently no way to reliably compare between MRI radiomics studies, because variations exist among all of them in MRI scanner sequence, scanner vendor, and scan acquisition parameters (90). We refer the interested reader to comprehensive reviews on the use of radiomics in the field of radiation oncology (90-93).

Quality assurance (QA)

Intensity modulation radiation therapy (IMRT) QA is labor-intensive and ML may improve the process efficiency. ML has been used to predict IMRT QA passing rates (94), error detection in radiation plans and delivery (95,96), and error prediction in image guidance systems (97). ML also has the potential to streamline the peer review QA process, which requires meticulous attention to detail and is time consuming for clinicians. It has been used for QA of both target/normal tissue contours and the final radiation treatment plan (98-100). ML has also been leveraged experimentally to correlate real-time dose deposition in proton therapy (101).

Two successive papers led by the University of California at San Francisco speak to the prodigious potential of DL for QA. In the first (94), the group led a multi-institutional effort to validate an ML algorithm for predicting 3%/3 mm gamma passing rates in IMRT plans. As previously mentioned, ML models learn from manually curated feature inputs, which in this circumstance were 78 features purposefully selected by expert physicists. Their ML model predicted passing rates within 3.5% accuracy for 618/637 IMRT plans, illustrating the potential for automation. Subsequently (102), they pitted their ML model against a repurposed DL neural network (AlexNet) that was originally trained on unrelated data and minimally retrained to predict gamma passing rates from raw radiotherapy fluence maps by altering about 4,000 of its network parameters. Despite that the model was not instantiated to interpret fluence maps and despite that the maps contained no curated features, the reconfigured AlexNet performed as well as the physicist-crafted ML algorithm.

Adaptive treatment planning support

Adaptive radiation therapy can be described as changing the radiation treatment plan during a treatment course in response to changes in anatomy (e.g., tumor shrinkage/progression, weight loss) or tumor biology (e.g., biomarkers). ML algorithms have been developed to identify patients that may benefit from adaptive re-planning for head and neck cancer and prostate cancer (103-105). ML algorithms for online adaptive magnetic resonance guided radiotherapy have been developed for patients with gastrointestinal cancers in which a daily optimized plan is generated before each treatment based on changes in anatomy seen on the magnetic resonance imaging scan (35,106). Interested readers are referred to a detailed review on the role of machine learning in adaptive radiotherapy (107).

A report by Fu *et al.* (35) illustrates the advantage afforded by DL for adaptive treatment. Radiation oncologists using an MRIdian MRI-linear accelerator (ViewRay Inc. Oakwood Village, OH, USA) at Washington University in St. Louis found that manual OAR contouring during adaptive online RT was onerous and had to be done manually. Therefore, a DL convolutional neural network (CNN) was developed to automatically segment liver, kidneys, stomach, bowel, and duodenum. To improve its accuracy, two additional CNN correction networks were integrated in the DL architecture and provided feedback that helped it learn anatomic constraints. The point of these correction CNNs was to learn spatial continuity information by sampling relatively large kernels (3×3×3 voxels) and use that to improve the output CNN contours. The CNN showed excellent DSC and HD results for the liver and kidney (immobile organs) but only fair results for the stomach, bowel and duodenum (mobile, spatially variable organs). Despite this limitation, the automated contours cut manual segmentation time by 75%.

Obstacles

Although AI technologies have proven to surmount many technical obstacles, significant political, legal, and ethical considerations remain to be resolved before widespread clinical implementation occurs.

A foremost concern is that the hidden neuronal architectures that afford DL such astounding predictive power are also its principle liability: DL is a "black box" in which predictions are made without human understanding of what features the network elects to use nor the exact statistical calculus by which it elected those features. This is a challenge to ensuring patient safety and clinician acceptance. Although the use of "saliency maps" (e.g., identifying the area of a chest X-ray which most contributes to the prediction) (108) are of benefit, this issue is not satisfactorily resolved (109). Other efforts have attempted to teach DL "common sense" (110). In reality, various automated clinical decision support systems (CDSS) that accomplish specific tasks as well as physicians have existed for 40 years, but clinical adoption has met skepticism (111). Physicians are distrustful of delegating consequential diagnostic and therapeutic decisions to CDSS that they do not understand. For this reason, clinician education in AI is highly salient to AI integration in clinical workflows. Incorporation of the concepts of AI into medical education, radiation oncology residency, and continuing education may accelerate the future of AI in healthcare (112).

As previously discussed, the accuracy of ML outputs depends directly on the quality and quantity of input data. Indeed, it is usually the training data, rather than the nuances of algorithm selection or mathematical parameters, that most profoundly influences the algorithm's generalizability and accuracy. Consider Google's highly accurate algorithm for detecting diabetic retinopathy, which was trained on a data set of 128,175 retinal images (98). This is a significant challenge in radiation oncology, where institutions are siloed and where institutional datasets are small. The best ML and DL algorithms will likely emerge from multi-institutional cooperatives. Nevertheless, multi-institutional data sharing will require standardized datasets and stringent privacy regulations. To obviate the need for securely sending and receiving HIPPA-sensitive datasets between institutions, an approach called distributed learning has emerged, in which data from multiple institutions are remotely and securely accessed without the data ever leaving the cybersecurity confines of its own institution

(113,114). Another possible approach (for DL only) is transfer learning, in which neural architectures are trained on very large datasets of unrelated data, and then retrained using a much smaller database of interest (transfer learning was exemplified in the discussion of repurposing AlexNet) (115,116). Additionally, the American College of Radiology has opened the Data Science Institute, which is hub for radiology professionals, industry leaders, government agencies, patients, and other stakeholders to collaborate and resolve obstacles to the development and implementation of AI. One of its express goals is to set standards for AI interoperability. This will help create an open source standard framework for AI use case development (117). Within radiation oncology, following a standardized nomenclature for radiotherapy planning structures ensures that data is FAIR (Findable, Accessible, Interoperable, and Reusable) (118) and easily computable. The American Association of Physicists in Medicine Task Group 263 report provides a framework for this nomenclature (119).

Finally, we echo a caution against possible unintended ethical consequences of ML, including the introduction of bias which could worsen health disparities (120). Since ML is only as good as the data we train it with—even data replete with our biases—we risk creating machines that are far more efficient and consistent at implementing our biases than we are. Furthermore, consideration must be taken to avoid introducing technologies that divide physician-patient relationships. The top-down, government-subsidized implementation of healthcare information technologies since the 2009 HITECH act has resulted in unanticipated and unintended consequences for physician burnout and patient "e-iatrogenesis" (121-124). Prudent AI use cases should be identified, and these should be modest, simple, and fluid with existing physician workflows.

Summary

We believe the literature evidence discussed above soundly supports our introductory assertion that radiotherapy treatment planning is primed to be revolutionized by AI. We have focused particularly on ML and DL AI use cases for hastening, increasing the quality, and decreasing the interobserver variability of image segmentation, treatment plan creation, QA, and patient-customized adaptive re-planning and treatment course personalization. AI has tested potential for advancing radiation oncology treatment planning, but significant challenges remain before its widespread implementation in the clinical setting.

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Footnote

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