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Artificial Intelligence in Radiation Oncology: Applications and Future Direction

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Abstract

The practice of radiation oncology is changing at a rapid pace. As models of care and department reimbursement change, departments are evaluating an increasing number of patients with complex medical backgrounds which must be acknowledged as increasing difficult treatment plans are developed. With altered fractionation strategies, compressed fractionation treatment delivery, and highly sophisticated radiation therapy treatment technology, radiation therapy has evolved into a highly rigorous discipline applying multiple overlapping image datasets to define targets of interest with sophisticated image guidance tools to ensure accuracy of therapy. Integrated with biomarkers associated with treatment response and therapeutic resistance, radiation therapy can be delivered to tumor with altered doses to image-guided subsets of disease. The datasets now required to generate radiation oncology treatment plans are becoming increasingly large and complex. Ultimately, artificial intelligence models will mature to ensure accuracy and consistency to department workflows and therapeutic decisions including contouring and treatment planning. Artificial intelligence can and will be applied to all elements of daily patient care as well as clinical translational research. In this paper, we explore how multiple components of artificial intelligence will support the radiation oncology work force and therapy-guided clinical trials moving forward.

Introduction

Artificial intelligence (AI) is described as the science and engineering of making intelligent machines and computer programs.[1] The field of AI combines increasing sophistication of computer science and the incorporation and integration of datasets to enable problem solving and translational research through computer-driven operations. In the clinical trial environment, investigators are expected to anticipate, during the clinical trial design, events that are predictable and how they should be managed if a patient is treated in a protocol compliant manner.[2] However, in the clinical trial setting or within daily department function, it is often an event or events, good or bad, that are unanticipated which require more detailed understanding of the data to determine root cause of the event and resolve problems or inconsistency in management. The data need to be reviewed and studied to determine if, whether or not, information in the patient history, genomic/proteomic biomarker assessment, or medical treatment de novo influenced the unanticipated outcome and whether or not the event could have been prevented with improved knowledge derived from AI models generated from established databases of patients treated in a similar manner. AI has two subfields: machine learning and deep learning. Although the terms are often applied in an interchangeable manner, there are nuanced differences. Both are sub-fields of AI and deep learning is a sub-field of machine learning. Machine learning is a human-driven process of pattern recognition designed to automate predictable and reproducible functions at a primary level. Deep learning is comprised of neural networks and the term “deep” refers to a neural network of more than three layers with a layer between input and output. Deep learning automates the process of features extraction, thus decreasing the human intervention required for machine learning and training. [3] Both processes leverage labeled datasets to inform and promote the computer algorithm. Machine learning requires human intervention, thus deep learning becomes a scalable form of machine learning. Both require structure with deep learning potentially providing an answer to a question that human intervention may or may not see. Most current AI programs function at this level. The next step in the development of AI is in the development of natural language processing including various data types including but not limited to molecules, images, and the grammar of software code. In this future capacity, AI may have the capability of identifying and anticipating what we do not yet see. Recent development of Chat Generative Pre-Trained Transformer (ChatGPT) and sibling models including Instruct GPT rely less on human intervention for activity but interpret words to generate a response.[4] The human training in ChatGPT is extensive and influences both input of information and response generated for the output of information, however it generates responses from training by calling upon multiple layers of input including context and tone, therefore generating more sophisticated responses than current engines managed exclusively by human input and output. This is referred to as a generative AI model. These datasets are trained on vast amount of information including the internet, websites news articles, scientific articles and more.[5] Generative AI also is provided periodic feedback for process improvements. These tools are not yet integrated into AI models in radiation oncology; however, it will not be long before generative models are integrated into our workflow providing checks and balances on our work and potentially serving as a mechanism for department and clinical trial quality assurance.

Radiation oncology heavily relies on computer data processing, making it a branch of healthcare that can greatly benefit from advancements in AI. Deep learning, or neural networks, is designed to emulate the human brain, and continuous advancements have the potential to surpass human intelligence. AI validation involves

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evaluating trained models on testing datasets, providing insights into the model's overall effectiveness and applicability. AI models will have influence in all aspects of radiation oncology. Today, nearly all AI programs in our discipline function at an early iterative level recognizing patterns in information and taught to recognize patterns and extract features based on what has been defined by specific human interactions. [6] By modern current standards the components are nascent however important to current daily department function. In the following sections, we will review current processes influenced by programs in AI and how they may be applied in the clinic today and in the future.

Administration and Regulatory Functions

The process of consult request in radiation oncology and obtaining information relevant for processing the consult have multiple predictable and reproducible steps which lend well to support from AI. AI programs currently exist and are applied routinely for customer satisfaction, and these can be re-purposed for chart preparation and consult.[7] The AI models at this level will permit departments and institutions to track demographics for referral patterns and additional information for growth of patient volume. The models will review information in the electronic medical record for chart completeness including regulatory compliance. This is important as electronic medical records including Epic do not have a module for radiation oncology. This is due to proprietary software imbedded within the electronic record in radiation oncology which direct and validate simulation, quality assurance computational components, and daily treatment. Because the software directly affects the function of the linear accelerator and quality assurance processes, accelerator companies such as Varian have not made the proprietary software available to electronic medical record companies such as Epic.[8] Therefore, institutions need to be creative in the development of interfaces to achieve the objectives for regulatory compliance for department processes. AI programs can provide cross reference within each record to facilitate transfer of objects between the systems. For example, Epic uses a program called Beacon for medical oncology. When radiation oncology departments are accredited for practice by the American College of Radiology (ACR) or the American Society for Radiation Oncology Accreditation Program for Excellence®(ASTRO-APEx), reviewers either onsite or using remote tools will only review objects from one electronic medical record. By default, the review must be from the electronic record in radiation oncology as it houses daily treatment quality assurance, daily treatment images, and computational analytics required for daily patient care. Interfaces, however, have imperfections and will both move unnecessary notes into the radiation treatment record and not move necessary notes [9]. This can often require human oversite to be certain the correct notes are in place at the time of regulatory review. AI models can align the correct note to the correct day which can in turn secure regulatory review and improve compliance to billing objects. Once key words can be incorporated into the AI models, the models can be re-purposed for department quality assurance regulatory compliance including insurance authorization. The standards for accreditation are increasing. Physician history and physical examinations and documentation are under significant scrutiny for regulatory and insurance compliance. Elements for a Level 5 consult can be reviewed by models for compliance. AI models can ensure key elements are addressed in a templated format to ensure compliance. The elements in a radiation oncology treatment chart including physics, treatment planning, simulation notes, on treatment visits, and completion/follow up summaries. AI models can identify gaps in documentation to improve compliance. Speech recognition technologies are a version of AI and coupled with templates, facilitate both compliance and throughput for document completion.[10]

These and other tools will prove invaluable to practice management teams as trends in volume can be managed in real time with direct feedback to providers and referral sites. The tools will make practices more efficient and increase vehicles and opportunities for communication between practices in order to facilitate department growth.

Patient Management

Modern radiation oncology requires metrics and pathways for patient management. Once a patient has agreed to therapy, the radiation oncologist needs to write a therapy directive for treatment and populate the record for directives for image guidance, dose volume constraints, and insurance approval. Many disease sites in radiation oncology have predictable metrics assuming normal functional anatomy. For example, prostate teletherapy with intensity modulation has dose volume constraints which often can be applied across a uniform patient population.[11] Therefore, dose to bladder, rectal, and small bowel volumes can often be applied in a uniform manner and AI models can be used to auto-populate documents at the discretion of the physician. These can be revised as needed for patient-specific issues including history of ulcerative colitis and other pre-existing medical comorbidities as needed by physician-specific interaction for dose volume adjustment for metrics. These models can be developed for all common disease sites with predictable structure and functional status including radiosurgery, brachytherapy, and all advanced technology radiation therapy forms of teletherapy. Often insurance directives request comparison of intensity modulation driven plans and plans developed with three dimensional technologies which can be a time burden on physics and dosimetry staff. AI models can generate these plans for comparison and review by insurance companies, saving both time and resources for providers of care allowing planning teams to dedicate more time to traditional work.[12,13] This has significant relevance to modern practice as even departments dedicated to advanced technology treatment delivery are often witnessing a selective general decrease in revenue per patient as compressed fractionation becomes a more common practice. Many departments are witnessing new patient growth which is required for budget however even these departments have a decrease in revenue per patient due in part to a decrease in the number of treatments despite an increasing number of patients. To maintain similar revenue and maintain cost despite increasing numbers of new patients, departments will need to apply AI tools to facilitate throughput and maintain quality with a similar number of staff. [14] This provides an economy of scale as AI models can direct and complete tasks with more predictable structure and endpoints and staff can monitor the AI models and devote time to tasks that are complex, less predictable, and mandate direct human intervention. [15]

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Segmentation, or contouring, is a crucial and essential step in radiation oncology. Accurate segmentation is vital because it determines the effectiveness of the treatment. The successful implementation of AI-based auto-segmentation was also demonstrated in prostate radiotherapy by Cha et al. [16]. Combining AI-based segmentation with the expertise of radiation oncologists can further enhance treatment efficacy and improve outcomes. Manual segmentation is very difficult in Neuroendocrine tumors, Santilli et al. successfully used nnU-net pipeline for automatic segmentation of tumor images, generating accurate segmentation masks.[17] Kazemimoghadam et al. utilized a deep-learning model on CT images of breast cancer patients and achieved promising results for accurate delineation of clinical target volume (CTV) [18]. An FDA-approved deep learning algorithm (VBrain) showed promising results for brain metastases segmentation.[19]

In radiation oncology, the likely most influential area AI models will impact in the next five years will be in image integration and radiation therapy treatment planning. Historically radiation therapy plans were developed using two-dimensional tools using fluoroscopy as the primary imaging vehicle [20]. Radiation dose was defined at the isocenter of the target and calculated to an isodose line. Today, radiation therapy is calculated to normal tissue and tumor volumes are contoured on three- and four-dimensional target volumes with objects superimposed of digital platforms. Dose is made uniform through the use of intensity modulation made facile by the presence of multi-leaf collimators housed within the gantry of the linear accelerator. However, the critical step for the radiation oncologist in the planning process is to contour the target volumes of interest including normal tissue for conformal avoidance and tumor targets for therapy. This is a critical component in treatment planning for radiation therapy. Today, the data sets for contouring targets are complex and often require multiple integrated datasets to complete contouring for patient care [21]. Radiation oncology today is an exercise in applied imaging. While the quality assurance of computational analytics and therapy delivery require significant quality assurance, the uncorrectable aspect to a radiation oncology treatment plan is the accuracy of physician contours.[22] If tumor is under contoured or disease over contoured into critical normal tissue, patient outcomes can be negatively influenced by disease progression or normal tissue injury. This is how radiation oncology has changed over the past several decades. Feasibility of auto-contouring of neovascular structure in prostate cancer patients was recently shown.[23]

CT and volumetric treatment planning have become the standard of care for patient management including clinical trials involving radiation therapy [24]. Each step in the process of image acquisition and contouring can be facilitated and assessed for quality assurance by models for AI. The radiation oncologist will write a simulation directive describing the goals and objectives of the simulation process and images required for fusion into radiation oncology planning images for contour definition. At this point images are obtained per physician directive at slice thickness commensurate with the objectives of the simulation. Historically, the work scope of the radiation oncologist often concluded with the completion of the simulation. Today, the work scope only begins with the end of the simulation hour. After an initial isocenter is placed, as a point of reference to accurately reproduce daily therapy, physics planning teams and the involved radiation oncologist develop a strategy for next steps in management. In an uncomplicated situation, often the objective can be directed to the task pad of the radiation oncologist for contour of targets. In multiple disease areas, however, fusion of additional images is essential for contour as many targets cannot be well visualized on radiation oncology planning CT studies, therefore targets need additional fusion of datasets to optimize contouring for patient care. Central nervous system management, especially targets for primary disease and for stereotactic radiation therapy require fusion of MRI objects to complete contouring in an accurate manner as often targets cannot be visualized on CT, even including contrast during the simulation. Future protocols for disease in the central nervous system will include multiple magnetic image datasets as, interestingly, each provides a different view of what could be tumor. For example, a modern protocol currently evaluates spectroscopy, fluid attenuated inversion recovery (FLAIR), and T1 signal with contrast to define targets with each area receiving a differential radiation dose using dose painting for treatment execution. Investigators are currently evaluating the use of positron emission amino acid imaging as a study to define the area of DNA synthesis within the tumor target as an additional area for therapy with augmented fractionation directed to the target volume defined by additional imaging tools. For contouring multiple datasets, registration and segmentation of images and targets requires precision and accuracy. AI models can both facilitate the processing of integrating images for target definition and ensure the accuracy of the integration of the datasets [25]. Multiple disease areas will be favorably influenced by AI models. Head and neck therapy is becoming increasingly significant for several reasons. The prevalence of this disease is rising, particularly among patients with viral etiology. Within this group, some patients experience positive outcomes and may benefit from tailored treatment adjustments. In a similar manner, investigators are evaluating the merits of volume titration in this disease to further promote improvement in normal tissue outcomes understanding the potential risk of recurrence in treating decreased volumes of both regional and primary target regions. Surgery is increasing in utility for this disease as it is often curative without additional therapy. In this circumstance, radiation therapy can be deferred until there is another event. In the event radiation therapy is recommended on a post operative basis, AI models can be used to define areas of risk at/beyond the surgical resection margin as well as additional lymph nodes at risk including sites of extra capsular extension [26]. This would further ensure targets at high risk will be incorporated into the therapy field and limit dose to targets of unintended consequence including the mandible, parotid glands, and spinal cord. There is increasing interest in titration of target volumes in head and neck cancer to limit long term sequelae of management. AI models have demonstrated potential in head and neck cancer [27]and hypopharyngeal cancer.[28] Datasets can be developed from benchmark cases and used as an atlas to compare individual cases to hone and improve AI models for target volume definition. Patterns of failure can be incorporated into the models to further refine the program for protocol management to learn what is reasonable for volume titration and what may place the patient at a higher risk of treatment failure. Pulmonary radiation therapy has undergone significant change in the past two decades. With increasing concern for toxicity associated with radiation therapy and systemic therapy

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including immunotherapy, investigators have placed cardio-pulmonary metrics into protocols which limit risk of a compromised normal tissue outcome. Tools such as positron emission tomography serve to further optimize target definition, additional regional nodal areas of risk and on occasion, additional primary disease. As tumor targets become better defined, it becomes increasingly difficult to treat the modern lung cancer patient to elective target volumes as meeting normal tissue constraints for cardiopulmonary function becomes increasingly difficult once all areas of metabolically active disease have been contoured. Motion management adds an additional degree of difficulty to the radiation therapy planning team as to accommodate this issue more normal tissue must be incorporated into the therapy field (ITV) to ensure full tumor target coverage. Recognizing this issue, AI models can serve to optimize planning in this situation and can recommend additional strategies of breath hold, adaptive planning from daily volumetric imaging, and driving dose through non-functioning sub-segments of pulmonary parenchyma defined on functional imaging fused into planning imaging.[29] These datasets will be large and not always intuitive to physics and physician therapy teams; therefore, AI will be required to identify both the time point and the strategy for when a meaningful change in target definition is needed to optimize patient care. Recently, AI was used in identifying dosimetric predictors of toxicity in cancer patients.[30]

Hepatic radiation therapy is becoming of increasing importance to the therapy community. The genesis of this disease is multifactorial in origin, however with a significant worldwide increase in incidence, therapeutic options need to be developed to improve patient care to this often-vulnerable patient population. With liver transplant a limited option for this patient population, local and systemic therapies are essential and often serve as a bridge to transplant when appropriate. There are several local therapies available to this patient population including ablation therapies and systemic radiation therapy, however each have challenges in treatment of the entire target with unintended dose delivered to normal tissue targets problematic for infusional and catheter directed radiotherapy with yttrium-90 (Y-90). Stereotactic radiosurgery applications have become an important component to the care of the patient with fractionation patterns directed by the volume of disease in juxtaposition to the volume of normal tissue parenchyma. Defining the volume of disease is challenging and often requires the use of multiple MRI sequences to define the target volume of interest. Often disease can be less conspicuous to reviewers, therefore AI models will help both define targets to treat, assign conformal avoidance strategies to functional parenchyma, and optimize radiation therapy treatment plans to achieve these important objectives. This area for radiation therapy has only recently matured as an important disease site for teletherapy including particles, therefore many radiation oncologists are less well versed in the challenges of target definition and treatment execution, therefore most radiation oncologists will benefit from both the development and utilization of these models to optimize patient care in this important area for stereotactic radiation therapy management.[31]

Additional areas of abdominal and pelvic disease are readily amenable to models for AI. Many abdominal/pelvic targets are optimally defined on alternate image sets. Mass lesions in the pancreas and extensions beyond the pancreas are often better defined on MRI. Fusion of data sets including AI auto contouring tools will optimize target definition for improvements in radiation oncology treatment definition and treatment delivery. Efforts to integrate stereotactic techniques into pancreas radiation therapy have only seen partial success due to challenges in accurately contouring and delivering radiation doses precisely across the duodenum.MRI has supported the development of targets within renal parenchyma for partial volume therapy in medically appropriate situations. Coupled with accurate motion management, these targets become important for radiation oncologists as the patient population is less amenable to surgical intervention. AI will optimize target definition and support conformal avoidance to functional parenchyma as partial volume renal therapy becomes of increasing importance. There are many situations today where endometrial and cervix brachytherapy cannot be performed secondary to medical comorbidities. Magnetic resonance can be used to define high risk areas of residual disease with radiation therapy treatment plans designed to provide dose painting strategies to both high and intermediate risk regions to provide care for the increasing patient population of those who cannot undergo anesthesia for brachytherapy. The integration of image sets with the development of teletherapy plans with intensity modulation using dose painting will be approached and facilitated by programs in AI as these plans become more commonplace and the therapy strategy becomes validated. Metabolic images including prostate-specific membrane antigen studies have provided improved definition of pelvic and abdominal lymph node regions improving target definition for regional therapy. As datasets build and can be applied for machine learning, the process of integrating AI models into daily workflow processes including planning and quality assurance.[10] Tozuka et al. recently developed a deep learning model, which showed improved gamma passing rates prediction.[32]

Conclusion

AI is of increasing importance in radiation oncology for many practical reasons. Modern therapy requires a significant skill set among physicians, physics planning teams, and therapy teams. It is difficult, if not impossible, for an average size department to recruit individual talent to provide expertise in all areas required for modern therapy. Reimbursement models in radiation oncology are also under change. Compressed fractionation strategies in common disease sites have altered the landscape of the financial infrastructure for the department. While departments may be evaluating more new patients as part of therapy management, department treatment numbers are not commensurate with the increase in new patient volume. Treatments, however, are more complex including modern image guidance, however reimbursement is not increasing in parallel with the complexity of therapy, therefore there is an increasing gap between the increase requirements for skill and therapy complexity with reimbursement. Radiation oncology departments are facing this dilemma and working to develop strategies to address this dichotomy. AI may help to address this gap by moving more repetitive department processes into models for AI. [33] A partial list of artificial intelligence programs available for use is seen in (Figure 1). Departments can facilitate this process by building internal datasets or using databases established by reliable platforms including the Imaging and Radiation Oncology Core (IROC) and The Cancer and Imaging Archive (TCIA). The future is bright for applying AI to all aspects of patient management in radiation oncology. We need to

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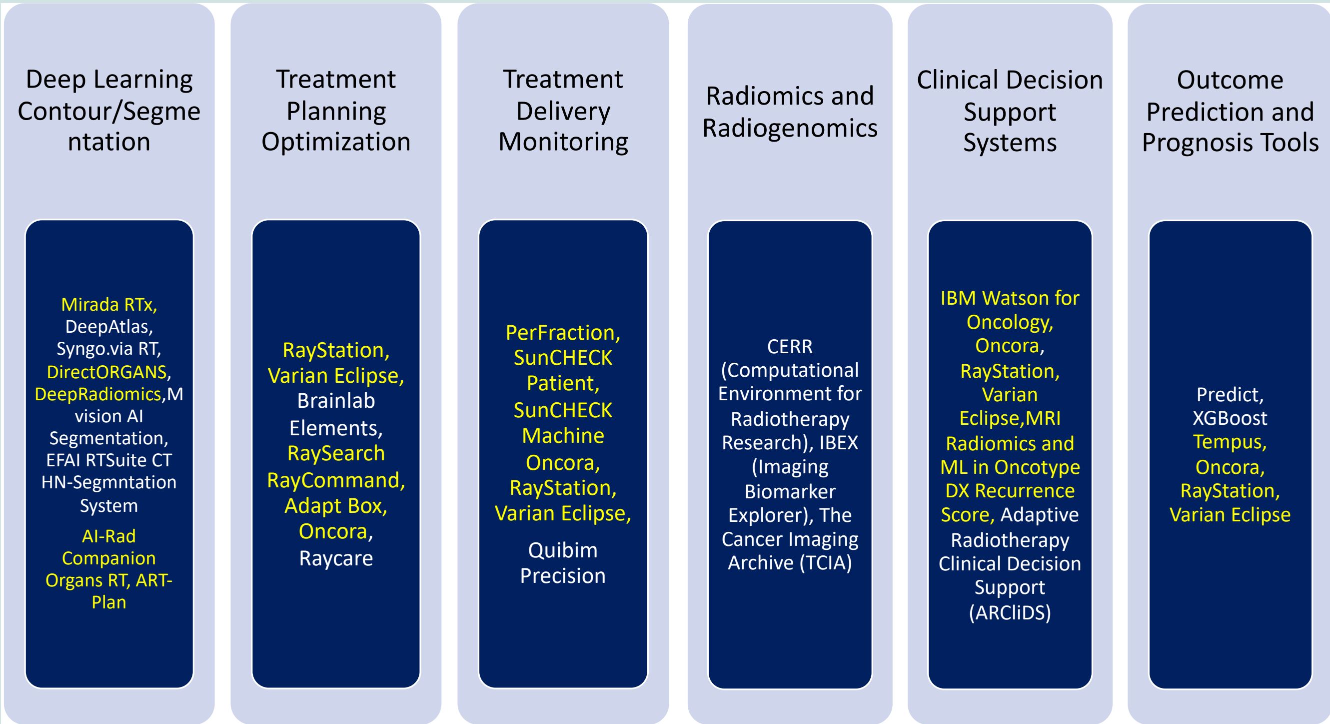

Figure 1: Partial list of available AI tools for radiation oncology.

remain disciplined in our approach and application of these models in order to optimize both workflow and quality assurance for the patients we serve.

Conflicts of Interest: The authors have no conflicts of interest to declare.

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