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Artificial intelligence plus molecular profiling for personalized radiotherapy: Questions 105–107 in the 150 most important questions in cancer research and clinical oncology series

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Abstract – Artificial intelligence (AI) has been increasingly applied in cancer prevention, diagnosis, prognosis, treatment planning, and therapy implications. For enhancing professional communication and promoting research collaboration, Visualized Cancer Medicine continues the program of publishing the 150 most important questions in cancer research and clinical oncology. In this article, we propose three new key questions about integrating AI into radiation therapy for cancer patients as follows. Question 105: How can we develop individualized radiation therapy based on the biological variations combined with AI analysis for better treatment outcomes and less treatment toxicity? Question 106: Can AI improve real-time dose monitoring and adjustments in radiotherapy? Question 107: Can molecular profiling plus AI be helpful for predicting the benefits of adjusting the plan in adaptive radiotherapy?

Key words: Personalized radiotherapy, Artificial intelligence, Molecular profiling.

Artificial intelligence (AI) has been increasingly applied in cancer prevention [1], cancer diagnosis and patient prognosis prediction [2], radiotherapy treatment planning [3], and radiotherapy implication [4]. In response to the call from Visualized Cancer Medicine for collecting the most important questions in cancer research and clinical oncology [5], the following three key questions are proposed in this article related to integrating AI into radiation therapy for cancer patients.

Q105: How can we develop individualized radiation therapy based on biological variations combined with artificial intelligence for better treatment outcomes and less treatment toxicity?

Most radiation therapy plans are optimized and reviewed based on dose-volume constraints recommended by guidelines, resulting in standardized plans. However, the sensitivity of different patients to radiotherapy is different. Even when treated for the same tumor type and with similar dose-volume parameters, the radiotherapy toxicity after treatment can differ significantly among individuals. Therefore, the "one-size-fits-all" approach is no longer the best treatment choice and individualized precision radiotherapy has gradually attracted attention [6]. The studies of low-dose radiation therapy (< 1Gy/fraction, LDRT) illustrate the discontinuity of the dose-response curve [7]. Preclinical studies and clinical radiotherapy have suggested that LDRT might have favorable immunological effects such as macrophage differentiation and an increased infiltration of effector immune cell [8, 9]. These biological factors, which are often ignored in the design of radiotherapy plans, can explain a more accurate dose-response relationship. Personalized treatment plans based on the individual characteristics of the patient and tumor have the potential to minimize toxicity and maximize benefit.

Recent research has incorporated biological response models, such as normal tissue complication probability (NTCP) and generalized equivalent uniform dose (gEUD), into the design of radiation therapy plans, to minimizing predicted radiation risks [10]. These studies offer a new perspective on personalized radiation therapy plan design and aim to improve treatment outcomes. Meanwhile, molecular profiling of the primary tumor, which may be associated with tumor radiosensitivity [11], is achievable via the application of minimally invasive biopsy coupled with high throughput sequencing, e.g., fine needle aspiration followed by various sequencing technologies [12, 13]. It is therefore reasonable to expect that molecular profiling of adjacent normal tissues to the tumor could be also achievable via similar technologies.

There are some challenges in integrating biological markers into the process of personalized radiation therapy: (1) Extract and select the biological markers related to tumor radiosensitivity or biological response. The large scale of basic

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information collected from one single patient could not be timely handled by human beings to keep the treatment plan executed within an acceptable time window. Artificial intelligence possesses efficient and powerful capabilities for large-scale data mining and analysis, and it has been used for disease diagnosis and prognosis prediction. We believe that, in the face of high-throughput biomarkers, the application of artificial intelligence is helpful to identify key relevant biomarkers. (2) Develop and validate algorithms for predicting the sensitivity of tumors and adjacent normal tissues to radiotherapy by combining the information from radiotherapy parameters and the molecular profiles of both primary tumors and normal tissues. The influence of biological markers on the dose-response relationship has not been clearly defined. Artificial intelligence, particularly neural networks, can fit nonlinear complex relationships to obtain prediction models with enhanced performance. However, during the validation and implementation of prognostic prediction models, it is essential to carefully consider that the variations in data sets might affect the model's generalization ability. If necessary, it is advisable to collect the local center's data set in advance for calibration. (3) Make the decision and design the radiotherapy plan based on models for predicting radiotherapy sensitivity. In the process of radiotherapy planning, prescription dose, dose fractionation, and limits for organs at risk are all related to radiotherapy sensitivity [14]. Artificial intelligence algorithms can effectively integrate multi-dimensional information and use the established accurate response model to provide more effective guidance, therefore obtaining plans that minimize toxicity and maximize the benefits of radiotherapy.

In summary, assistance from artificial intelligence is therefore expected to accelerate the whole procedure. Artificial intelligence algorithms can facilitate the completion of complex and time-consuming tasks, such as the processing of large-scale molecular profiling data and the rapidly delineating regions of interest. Additionally, they can aid in modeling and decision-making, thereby enhancing the accuracy of radiotherapy and improving potential treatment outcomes. Combining molecular profiling and artificial intelligence should pave the road for future personalized radiotherapy treatment planning based on biological variation with better treatment outcomes and less treatment toxicity.

Q106: Can artificial intelligence improve real-time dose monitoring and adjustments in radiotherapy?

An optimal radiation therapy plan can achieve excellent outcomes only when executed accurately. However, during the implementation of the plan, various factors – such as organ movements (e.g., respiratory motion, gastrointestinal peristalsis), mechanical errors, and positioning discrepancies – can lead to deviations of the target area from its intended location, and the irradiation of normal tissues with high doses. Consequently, monitoring these changes throughout the therapy process and ensuring the precise execution of the plan is crucial for achieving effective treatment outcomes. Current strategies commonly involve controlling and tracking target movements to maintain anatomical positioning as closely as possible to the planned. Nevertheless, the actual dose delivered to the patient remains unknown with these methods. Additionally, many tracking techniques are invasive, which restricts their application.

With advancements in the field of computer vision, artificial intelligence is expected to improve real-time, non-invasive target tracking, dose reconstruction, and treatment plan adjustment [15]. Markerless tracking, which utilizes deep learning utilizing various types of real-time medical images such as ultrasound, 4D CT, and X-ray, has been reported in numerous studies [16–18]. Additionally, accurate and rapid motion prediction algorithms can be used to deal with the delays caused by system positioning and action time. Compared to traditional dose calculation algorithms, dose reconstruction based on artificial intelligence is faster and can satisfy the time constraints required for real-time plan adjustments [19]. The radiotherapy plan optimization and adjustment technology based on artificial intelligence exhibits similar dosimetric parameters while requiring less time compared to conventional techniques [20, 21].

In addition, anatomical changes, such as tumor shrinkage and weight loss, during the radiotherapy treatment process could result in normal tissues and organs at risk of being involved in the high-dose irradiation area, thereby increasing radiation toxicity. The application of artificial intelligence technology to predict or monitor anatomical changes can assist physicians in quickly determining the actual dose distribution based on the predicted anatomical changes. This information is crucial for assessing whether the radiotherapy plan needs to be adjusted according to the dose received by normal tissues. Lee et al. [22] developed a ConvLSTM model to predict the deformation vector fields (DVFs) in the subsequent CT images based on the planning CT and weekly CBCTs, and then designed and adjusted the adaptive plan based on these DVFs.

The radiosensitivity of tumor tissues for the same patient changes dynamically during radiotherapy. With advancements in biological imaging techniques, including functional imaging, molecular imaging, and metabolic imaging, we are expected to visualize the physiological and metabolic changes in tissues and cells during radiotherapy. These imaging techniques help workers identify regions that require high doses more accurately [23], while artificial intelligence algorithms can help to explore the critical connections within the workflow. For instance, artificial intelligence tools can efficiently and accurately perform automatic delineation of target volumes combined with PET/CT imaging to determine precise target volumes [24]. These technologies are anticipated to provide an effective technical foundation for real-time dose detection and plan adjustment, however, their stability and clinical applicability still require further investigation and validation.

Q107: Can molecular profiling plus artificial intelligence be helpful for predicting the benefits of adjusting the plan in adaptive radiotherapy?

During radiotherapy treatment, anatomical changes such as weight loss, shrinkage of tumor volume, and physiological movement of organs at risk may occur. Adaptive radiotherapy has been proposed and applied in clinical to adapt to these changes and the main goal is to ensure target coverage and reduce treatment toxicity. While adaptive radiation therapy (ART) improves patient outcomes [25], it requires re-delineation of target areas and the re-optimization of treatment plans, resulting in additional workload for practitioners as well as higher time and economic costs [26, 27]. This complexity poses challenges for the broader adoption of this technology.

Currently, the decision to implement ART is contingent upon the degree of target area shrinkage and anatomical changes observed in current versus planned imaging, relying heavily on experience and subjective judgment. Some patients may experience minimal changes in treatment outcomes, such as tumor control or normal tissue toxicity, before and after adjustments, which can lead to wasted treatment time and resources [28, 29]. Therefore, predicting the patient benefits at the time of adaptive planning adjustments is a critical issue that requires further research.

For this purpose, more accurate dose-response prediction models for the treatment targets and surrounding normal tissue are needed [30]. Meanwhile, biological and molecular responses often precede the anatomical changes suggestive of ART and molecular profiling may provide clinically relevant prognostic information [31]. With the advances in tumor analysis next-generation sequencing and other profiling technologies [32], we believe that molecular profiling of the treatment targets as well as the adjacent normal tissue might be helpful for generating more accurate predicting algorism. In the interest of efficiency, artificial intelligence is again expected to play a critical role in conducting in-time dose-effect analyses prior to plan adjustment, which can promote adaptive planning to a more accurate level.

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Conflicts of interest

The authors declare that they have no conflicts of interest in relation to this article.

Data availability statement

Data sharing is not applicable to this article.

Author contribution statement

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Ethics approval

Ethical approval was not required.

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