"Artificial Intelligence in Radiotherapy and Radiopharmaceutical Development: Shaping the Future of Medical Physics and Smart Design"

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Abstract :-*Artificial Intelligence (AI) has become a pivotal force in advancing radiotherapy and radiopharmaceutical development, enhancing precision, efficiency, and personalization in cancertreatment. In radiotherapy, AI-driven tools optimize treatment planning by accurately predicting tumor response, automating contouring of target volumes, and adjusting treatment parameters in real-time to accommodate anatomical changes during therapy. AI algorithms improve dose distribution and minimize radiation exposure to healthy tissues, thereby reducing side effects and improving patient outcomes.*

In radiopharmaceutical development, AI accelerates the discovery and design of novel radiotracers by analyzing complex datasets and predicting biological behavior and pharmacokinetics. Machine learning modelsidentifypotentialtargetsandoptimizemolecularstructuresforbetterdiagnosticandtherapeutic *efficacy. AI also facilitates the integration of imaging data to monitor treatment response, allowing for adaptive strategies that enhance therapeutic effectiveness.*

Keywords: ArtificialIntelligence,RadioTherapy,Radiopharmaceutics

Introduction:

The incidence and death of cancer are rising quickly, making it a serious threat to human life. The use of targeted therapy in conjunction with diagnostic imaging is growing in popularity as doctors look for noninvasive ways to examine tumour morphologies and assess functional and molecular responses to treatment [1]. Radiotherapy has a history of improvement along with the advances in diagnostic imaging. With the advent of computed tomography (CT), the ability to depict tumors not as shadows but as 3D structures has advanced radiotherapy from 2D to 3D.[6]Medical physicists play a critical role in radiation therapy by contributing to the processes of simulation, treatment planning, dose delivery, and post-treatment follow-up [2].The adoption of AI in radiotherapy has become increasingly important due to the time-consuming nature of radiation therapy workflows. These workflows require extensive manual input from medical physicists, radiation oncologists, dosimetrists, and radiation therapists, further compoundedby the growing prevalence of cancer. AI offers significant advantages by reducing the need for human intervention, decreasing workload, and minimizing biases in treatment techniques, thereby enhancing plan quality and improving the accuracy and efficiency of treatment planning [3-5]. AI was first introduced in 1956 during the Summer Research Project held at Dartmouth College in the United States [3, 4].For instance, AI enables data from computed tomography (CT) scans to be instantly uploaded to a treatment planningsystem,eliminatingtheneedformanualdosecalculations.Moreover,incasesinvolving complex body tissues with multiple cross-sections, computerized planning systems utilizing dose distributionalgorithmsprovidegreateraccuracyandfeasibilitycomparedtomanualcalculations. However, those responsible for planning treatments often have limited familiarity with the theoretical principles underlying these algorithms. As a result, individuals other than medical physicists who perform treatment planning tasks are likely to become experts in these operations. Consequently, the role of the medical physicist may shift away from direct involvement in treatment planning procedures [6].

A common tool for treatment planning is the image registration-based approach. This method utilizes a reference set of images, known as an atlas, with predefined organ contours. When a new image is introduced, it is matched to the reference images using registration algorithms. The contours from the reference images are then transformed onto the new image based on the registration results. However, the effectiveness of this approach depends on various factors, such as the choice of atlas and registration method.Humanverificationandcorrectionsremainnecessary,ascurrentautomaticsegmentation methodslacktheintelligencetofullyemulatehumanexpertise.WithadvancementsinAI,thereis potential for mimicking human decision-making, particularly in accurately contouring lesions and organs.

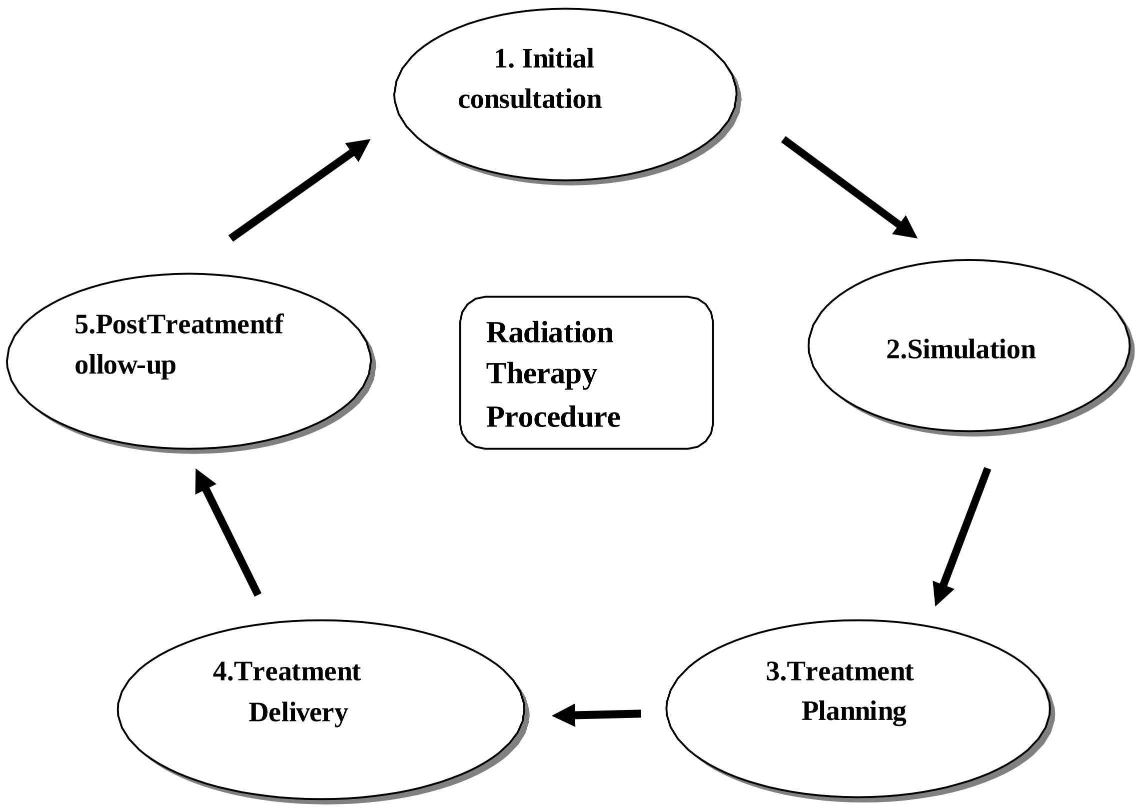
Treatment planning, meanwhile, is a collaborative human-computer interaction aimed at solving an optimization problem. The objective is to create an effective treatment plan where the prescribed dose is delivered to the tumor while minimizing exposure to surrounding healthy tissues. In this process, humans define initial optimization goals—such as the minimum dose to the tumor, tolerated doses for normalorgans, and optimization weights—while the computer adjusts treatment parameters, including linear accelerator (LINAC) gantry angles and multi-leaf collimator shapes, to meet these goals. Humans then evaluate whether the plan achieves the desired outcomes and adjust goals as needed. This process heavily relies on the planner's experience, introducing variability and uncertainty in treatment quality. AI, with its abilitytoemulatehumanthoughtprocesses,offersapromisingalternativetoenhancedecision-making and standardize treatment planning.

Quality assurance (QA) is another critical component in radiotherapy, ensuring that equipment and procedures meet specified standards. Radiotherapy involves various equipment, such as LINACs, simulators, and laser positioning systems, as well as multiple steps, including CT scanning, tumor identification, and treatment plan optimization. Errors in any equipment or step can pose significantmedical risks. QA aims to minimize these risks but is influenced by human-dependent factors that canaffectprecision. Furthermore,complex QA procedures create additionalworkload for clinics and reduce the time available for equipment to be used in treatment. There is a growing need for QA processes to be more accurate, efficient, and standardized. AI, with its ability to perform tasks with human-level intelligence, presents a compelling solution for improving QA in radiotherapy.

Given the significant potential of AI in these three aspects of radiotherapy—segmentation, treatment planning, and quality assurance—it is being actively explored to enhance quality, standardization, and efficiency [7-12].

Atranslatableradiopharmaceuticalischaracterizedbyitshighaffinityforthetarget,minimalnon-specificbinding,andfavorablepharmacokinetics.Whetherthecompound'sstructureisnovelor resembles an existing one, significant effort is needed to ensure its optimal performance. However, even withmeticulousdesign,thereisaconsiderablechancethatthecompoundmayfailtoeffectivelyengage its target in vivo due to unforeseen factors that were not accounted for during the development phase [13].

Fig.1StepsinvolvedinRadioTherapy:



Growing numbers of patients, higher demands for quality like early detection and personalized therapies andanincreasingworkloadformedicalandnursingstaffcreatesademandforautomationandtheneed for extracting more information from acquired data. Potential advantages of AI are already visible in screening routines in which a high number of patients (and associated data) are investigated for thepresence or absence of disease, with results that are not worse than human performance. For example, McKinneyetal.wereabletoshownon-inferiorityoftheiralgorithmforscreeningofbreastcanceras compared to experienced radiologists [14]. At the same time, AI results are being criticized because of the lack of transparency and consequently a potential lack of reproducibility [15]. The introduction of AI into the operation of radiology departments has led to optimizing resources [16]. Such operational AI should prove even more relevant in nuclear medicine (NM), which deals with radioactive isotopes, whose shelf-life is limited.

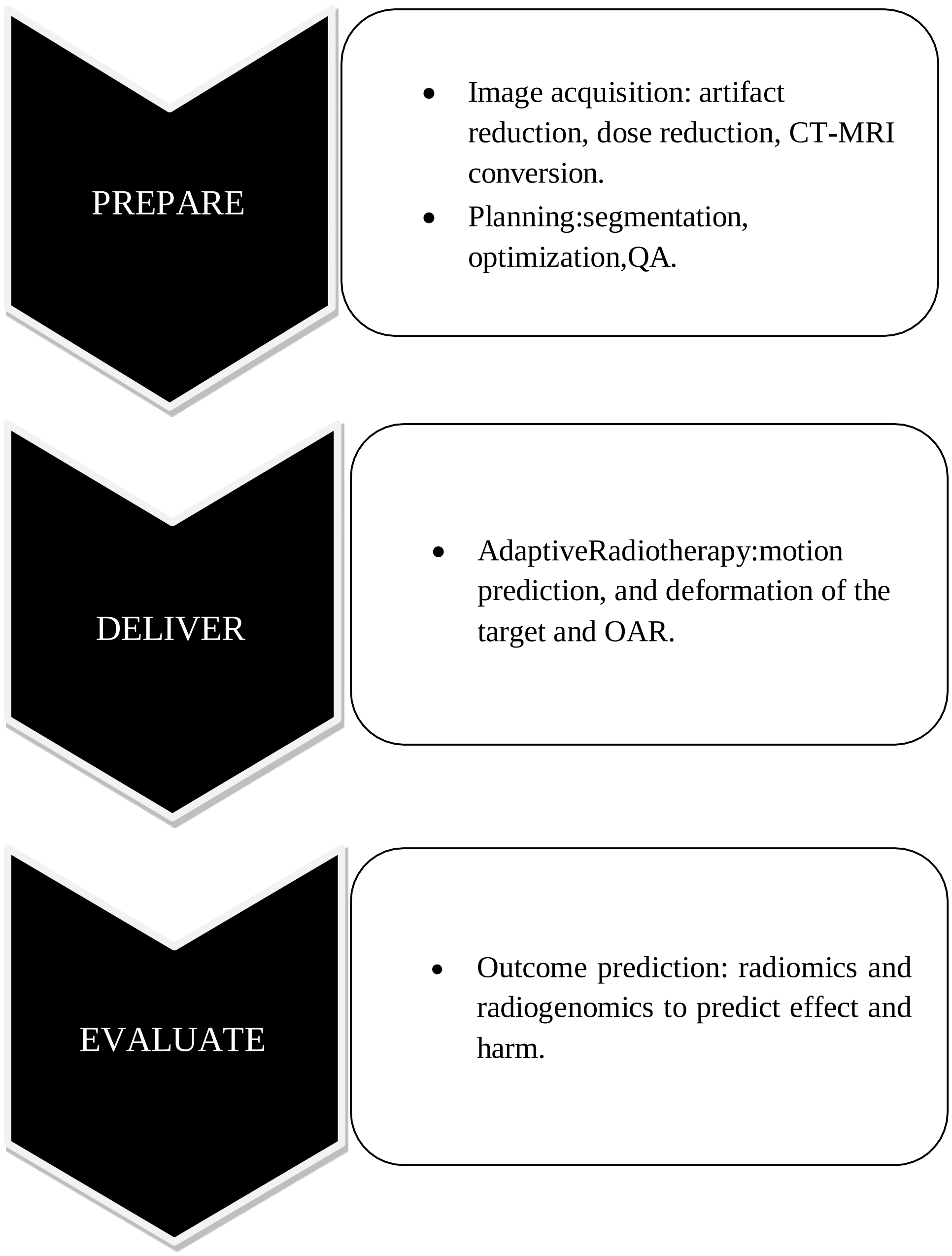
UsingAItoPredictPrognosis:-

In recent years, there has been a significant increase in reports on radiomics and prognostication,particularly in the field of radiotherapy. While many studies have focused on lung cancer and head andneck cancer, rectal cancer remains the most widely studied when compared to overall survival (OS).[17-22]. This trend can be linked to the National Comprehensive Cancer Network (NCCN) guidelines, which advocate for concurrent chemoradiotherapy followed by surgical resection in cases of locally advanced rectal cancer. This recommendation is supported by a systematic review conducted by the ColorectalCancer Collaborative Group, which found that preoperative radiotherapy significantly lowers the risk of localrecurrenceand mortality in rectalcancer,especially inyoung,high-risk patients [23-24]. Asa result ofthisapproach,patientswithlocallyadvancedrectalcancertypicallyundergobothpretreatmentand post treatment MRI scans, along with pathological assessments. The current focus is on determiningwhetherpathologiccompleteresponseatsurgery canbepredictedusingpre-orpost-CRTimaging[25-26].

Numerousstudieshavedevelopedpredictionmodelsbasedontextualfeatureswithinretrospective, single-institution analyses, utilizing T2-weighted (T2W) images or diffusion-weighted imaging/apparent diffusion coefficient (DWI/ADC) maps in MRI. These studies typically employ training and validation datasets. While some have reported highly promising results, the regions of interest (ROIs) are often delineated manually. Furthermore, the single-center design and lack of external validation limit the generalizability of these models, making it challenging to establish a standardized approach for assessing radiomics efficacy with the currently available data.

To addressthese limitations, manual segmentation canbe replacedwith automatedmethods.Forinstance,a recent study by Lietal.introducedan automated pipeline that integratestumor segmentationand outcome prediction using pretreatment MRI. In this approach, segmentation was performed using a U-Net model with an encoder-decoder structure, and a three-layer convolutional neural network (CNN) was usedtobuildpredictionmodels.ThepipelineachievedaDicesimilaritycoefficient(DSC)of0.79for segmentation,acompleteclinicalresponse(cCR)predictionaccuracy of 0.789,aspecificity of0.725,and a sensitivity of 0.812 [27-30].

Fig.2Processofapproach



ApplicationofAIinRadiotherapyPractice

Due to its capacity to provide a realistic physical interaction process in biological tissues, Monte Carlo(MC) simulation has been recognised as the target standard for treatment planning techniques in radiation therapy.However,thesesimulationsrequirealargeamountofcomputinganddatastoragepower,are time-consuming, and are complicated. AI can deliver more effective, convenient, and customisedtherapeutic practice in less time by using patient data [31].

Radiomics: extraction of features from diagnostic images, the final product of which is a quantitative feature/parameter, measurable and mineable from images. A Radiomics analysis can extract over 400 features from a region of interest in a CT, MRI, or PET study, and correlate these features with each other andotherdata,farbeyondthecapability of thehuman eye orbrain to appreciate.Suchfeatures may be used to predict prognosis and response to treatment [32-33].

ChallengesInRadiopharmaceuticalDevelopmentandPreclinicalEvaluation

Radiopharmaceuticalsareradiolabelledformulationsorprecursorsusedinthepracticeofnuclear medicine for diagnostic, therapeutic, and disease surveillance purposes, as well as for research tools in the pharmaceutical industry [34].

Preclinicalevaluationisanintegralpartoftheradiopharmaceuticaldevelopment.Overtheyears, advancesinbiologyandchemistry-relateddisciplineshaveledtotheuseofvariousmoleculestodevelop a new generation of radiopharmaceuticals whose purpose is to deliverradioisotopes to specific targetsatthe cellular or molecular level. This necessitates a thorough evaluation of radiolabelled molecules duringthe preclinical stage to assess their safety and suitability for the intended clinical application.

Targetidentification

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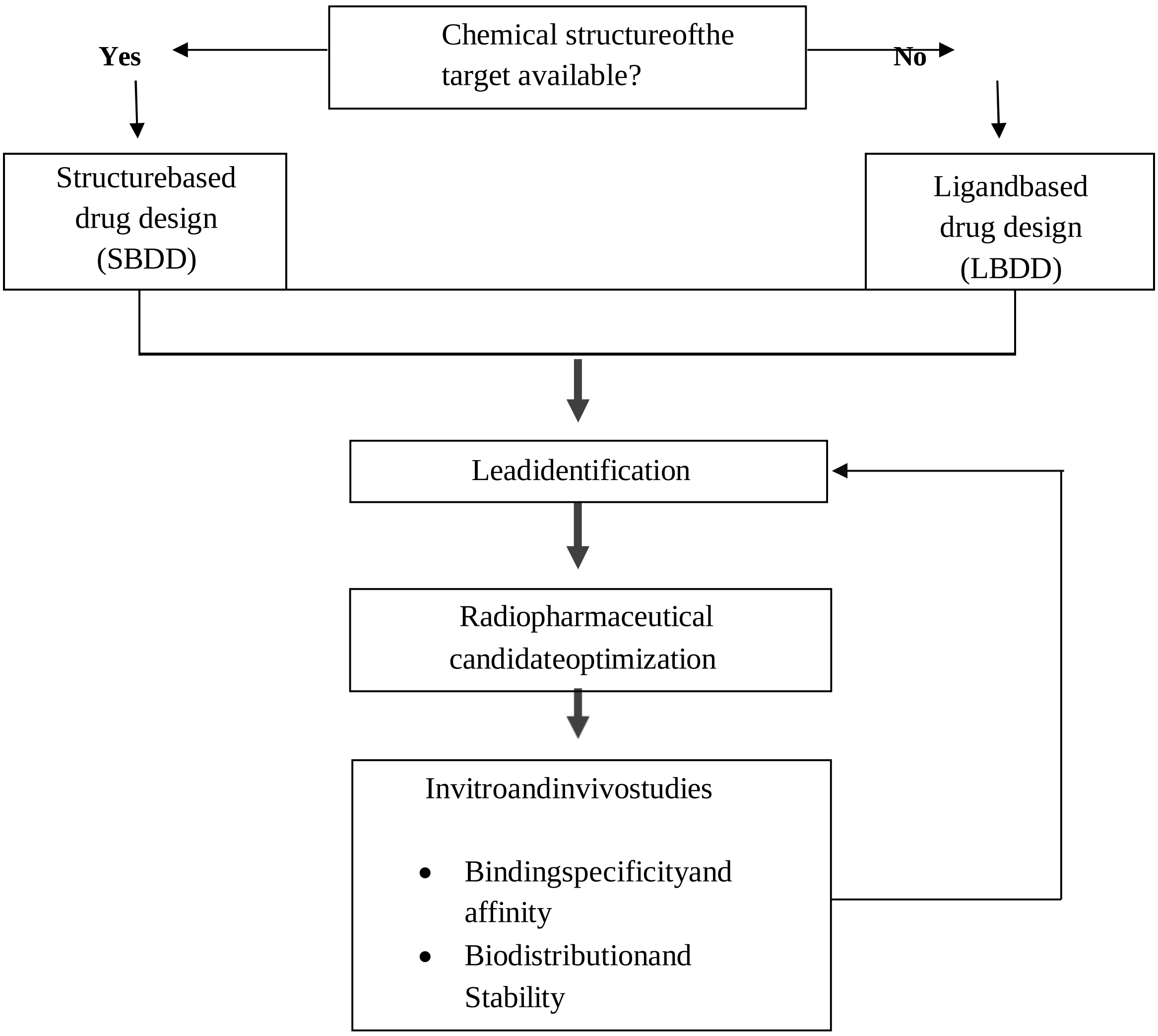

Fig.3 Basic workflow of structural computational modeling techniques in radiopharmaceutials design and optimization

TheFutureofAIinRadiationOncology:PotentialContributionsandNecessaryAdvancements

AIoffersthesignificantadvantageofdrasticallyreducingthetimerequiredforsegmentationand treatment planning. However, addressing inter-observer variability in tumor segmentation remains a key challengeatthisstage.WhileAI-basedsegmentationoforgansatrisk(OARs)ishighlybeneficialin daily clinical practice, it also holds potential for standardizing treatment protocols in large-scale clinical trials.

Forexample, a study utilizing data from the RTOG0617 trial, which investigated the effect of radiationdose escalation on overall survival (OS) in patients with inoperable non-small cell lung cancer, demonstrated this potential. Thor et al. compared manual cardiac segmentation performed during the trial with auto-segmentation using a deep learning algorithm. Their findings revealed that cardiac doses calculated via auto-segmentation were generally higher and showed a stronger correlation with OS than those obtained through manual segmentation in the clinical trial [35]. Radiotherapy planning aims to standardize tumor dosing while imposing constraints on the dose delivered to organs at risk (OARs). However, variations in segmentation during the initial stages can impact the evaluation of treatment outcomes. In clinical trials, significant time is often spent centrally reviewing and standardizing treatment plans. Achieving automated OAR segmentation with dose constraints could not only simplify datacollection but also improve the accuracy of treatment efficacy evaluations. Additionally, this approachcould enable a more precise assessment of dose adequacy and provide a basis for determining appropriate prescribed doses tailored to tumor heterogeneity.

Using MRI for treatment planning offers the advantage of avoiding unnecessary radiation exposure while enablingaccuratecontouring ofcomplex structures,suchastherectum anduterus,which arechallenging to delineate with CT. However, MRI-based planning requires the conversion of MRI images to electron density maps, as there is no straightforward method to directly correlate electron density with MRI signal intensity. AI-driven CT-MRI conversion is being actively developed to address this limitation [36-37].

Severalchallengesremaintobeaddressed,suchasvariationsinbonedensity amongindividuals. However, advancements in MRI-to-CT conversion research may make it possible to clearly delineate soft tissue boundaries—such as the rectum and other structures—by detecting subtle density differences in CT images, similar to the capabilities of MRI. This could enable MRI-level segmentation accuracy even in countries with limited medical resources, where treatment planning relies solely on CT. The successful integration of AI into radiotherapy holds the potential to standardize cancer treatment globally, ensuring equitable access to high-quality care [38].

1. ChallengesinCurrent Practices

- Variabilityin Bone density among individuals.
- Difficulty in Soft Tissue delineation with CT.

2. Advancements in MRI -to-CT conversion

- AIResearchin MRI-to-CT Conversion.
- Improved Soft Tissue boundarydetections in CT images (similar to MRI capabilities).

3.PotentialOutcomes

- MRI-level Segmentation accuracyachievedwith CT.
- Enhanced treatment panning in Resource-limited settings using CT.

4.GlobalImpact

- Standardised cancer treatmentworldwide
- Increasedaccesstohigh-quality radiotherapy in under-resourced regions.

Another promising area in radiotherapy (RT) is the development and application of large-scale language models(LLMs).Languageunderstandinghaslongbeenacentralfocusin AIresearch,evolvingfrom early rule-basedsystemstotoday's highly advancedmodels.LLMsaredesignedtolearnpatternsfrom vast amounts of textual data, enabling them to understand and generate natural language with remarkable accuracy. Significant advancements in LLMs have been achieved, particularly in recent years. A notable example is the Generative Pre-training Transformer (GPT) series developed by Open AI. Since the introduction of the original GPT model, subsequent iterations—such as GPT-3 and GPT-4—have demonstrated rapid advancements in scale and capability [39-40].The rapid advancements in LLMs have equipped these models with highly sophisticated capabilities in understanding and generating natural language.Thishasenabledawiderangeofapplications,includingquestion-and-answersystems, document creation, code generation, and even creative tasks such as poetry and storytelling.

In the medical field, the potential of LLMs is increasingly being recognized, with applications expanding across various areas. These include providing diagnostic support, generating and organizing medical documents, aiding in research, assisting in drug selection, supporting telemedicine, analyzing medical images, enhancing medical education, promoting preventive healthcare, improving lifestyles, and contributing to the design and analysis of clinical trials [41-42].

TheapplicationsofLLMsareenabledbytheirabilitytoidentifypatternsinlargedatasetswhile generating natural language outputs. However, challenges persist in their use within the medical field.Theseincludeconcernsoverdataprivacy,modelinterpretability,risksofmisdiagnosisand misinformation, and issues with consistency. Addressing these challenges, including mitigating "AI hallucinations",requires not only technological advancements but also the establishment of appropriate regulations and guidelines.

In radiotherapy, the continued development of LLMs holds significant promise, particularly in prognosis prediction. This will involve integrating diverse data types beyond imaging, such as information on concomitant medications and other patient background details, to build comprehensive datasets. Additionally, LLMs could predict adverse events and treatment effects while also serving roles in preliminary consultations. They may further contribute by disseminating information to patients,simplifying medical terminology, and addressing frequently asked questions, enhancing both clinical practice and patient engagement [43-45].

Barriers to AI in radiology & challenges

Data-sets & training

The availability of large amounts (big data)of medical images in the imaging domain (from PACSsystems) offers great potential for AI training, but such data need a so-called “curation” process in whichthe data are stratified by patient cohorts, segmented to extract the region of interest for AI interpretation, filtered to assess the quality of acquisition and reconstructions, etc [46].

Conclusion:

The integration of artificial intelligence (AI) into radiotherapy (RT) marks a transformative shift in how cancer treatments are planned, delivered, and evaluated. AI's ability to streamline processes, enhance precision, and reduce the workload has already demonstrated its potential to revolutionize RT. From outlining complex anatomicalstructuresandautomating treatmentplanning tooptimizing dosedelivery and monitoring patient responses, AI offers a level of accuracy comparable to manual procedures but at a fraction of the time required. This time efficiency not only improves operationalworkflows but alsoensures timely interventions, which is critical in cancer care.

Despite these promising advancements, challenges remain in fully harnessing AI's capabilities in RT. Oneof the primary hurdles is ensuring quality assurance (QA) for AI systems, which can be demanding and requires significant involvement from clinical medical physicists. To address this, academic institutions must integrate AI-related content into their medical physics curricula, ensuring future professionals are equipped to handle these advanced technologies. Furthermore, manufacturers of radiotherapy equipment must collaborate closely with qualified medical physicists to incorporate AI tools into their systems while adhering to stringent safety and accuracy standards.

AI’s application in RT spans numerous areas, including organ-at-risk (OAR) and tumor segmentation, treatment planning, and QA processes. These advancements have demonstrated significant improvementsinperformance,timeefficiency,andworkloadreduction,enablingclinicianstofocusmoreonpatient care. However, the technology is still in its early stages, with challenges such as interpretability, accuracy, and data privacy requiring further research and refinement. Addressing these issues will be critical in expanding AI’s role and ensuring its reliability in clinical practice.

Beyond automation, AI offers immense potential in advancing precision radiotherapy. By integrating data beyond imaging—such as patient backgrounds, concomitant medications, and other clinical factors—AIcan support more accurate prognosis predictions and personalized treatment planning. Additionally, AI'sroleinadaptiveradiotherapy,whichadjuststreatmentinreal-timebasedonpatientresponses,highlights its ability to delivermore targeted andeffective care.Withtheincorporation of large-scalelanguage models (LLMs), AI could further enhance patient engagement by simplifying complex medicalterminology, addressing common inquiries, and guiding patients through their treatment journeys.

The future of AI in RT lies not only in improving technical workflows but also in enhancing the patient experience. By automating processes such as segmentation, optimization, and data collection, radiation oncologists can allocate more time to patient interactions. This shift will allow for more meaningful conversations, fostering trust and improving treatment outcomes. Moreover, AI's potential to support prevention, diagnosis, and treatment extends its impact beyond RT, contributing to the broaderdevelopment of precision oncology.

Inconclusion,whilechallengesremain,theintegrationofAIintoradiotherapyrepresentsasignificant step toward standardizing and optimizing cancer care. Continued research and collaboration across academic, clinical, and industrial sectors are essential to address current limitations and unlock the full potential of AI in RT. As these technologies evolve, they promise not only to enhance treatment accuracy and efficiency but also to improve patient outcomes and the overall quality of care in oncology.

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