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Review Article

Application and progress of artificial intelligence in radiation therapy dose prediction

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ABSTRACT

Radiation therapy (RT) nowadays is a main treatment modality of cancer. To ensure the therapeutic efficacy of patients, accurate dose distribution is often required, which is a time-consuming and labor-intensive process. In addition, due to the differences in knowledge and experience among participants and diverse institutions, the predicted dose are often inconsistent. In last several decades, artificial intelligence (AI) has been applied in various aspects of RT, several products have been implemented in clinical practice and confirmed superiority. In this paper, we will review the research of AI in dose prediction, focusing on the progress in deep learning (DL).

Introduction

Since the beginning of last century, RT has completed the evolution from two-dimensional (2D) to three-dimensional (3D) conformal radiotherapy technology to Intensity-Modulated Radiotherapy (IMRT). Presently, IMRT is widely used in clinical practice, which includes multiple variants (fixed beam intensity-modulated radiation therapy, volume intensity-modulated radiation therapy, and tomographic radiation therapy, etc.).IMRT as one of the three-dimensional conformal radiation therapy, is superior in terms of uniform radiation dose to planning target volume (PTV) and protection of organ-at-risks (OARs) [1].In order to achieve individualized and precise radiotherapy, minimizing normal tissue damage while persevering sufficient tumor control is crucial [2].Planners often need to perform multiple rounds of parameter adjustment in a trial-and-error manner to achieve the optimal dose distribution. This process is time-consuming, labor-intensive, and may delay patient treatment, leading to poor prognosis [3,4]. Furthermore, the quality of the final dose distribution delivered varies significantly as a result of differences in knowledge and experience from different institutions or individuals [5]. The widespread use of AI will have the opportunity to change that.

AI, a branch of computer science, produces a new kind of intelligent machine that can respond in a similar way to human by understanding the nature of intelligence. Research in this field includes robotics, speech recognition, image recognition, natural language processing, and expert systems. Machine learning (ML) as a branch of AI., it trains the model by selecting an appropriate algorithm, and obtains the model by automatically analyzing the data, so that the model can be used to predict the unknown data. The pivotal concept of machine learning is to generate accurate predictions after training on a limit learning dataset. Since the DL based on CNN won the ImageNet [6], it has made outstanding achievements in various fields including medicine in last ten years with the massive use of computers and the growth and explosion of data [7]. Among them, the convolution neural network (CNN) it contains is the most common neural network that has been applied to image analysis, which plays the same pivotal role in the field of dose prediction.

The combination of AI and dose prediction is not only expected to improve the poor prognosis of patients due to delayed treatment, but also improve the consistency of treatment plan among individuals and even between institutions, thus realizing the standardization of tumor radiotherapy. This paper reviews the application of AI in dose prediction, focusing on the research progress of DL in this field in recent years.

Abbreviations: RT, radiation therapy; AI, artificial intelligence; DL, deep learning; 2D, two-dimensional; 3D, three-dimensional; IMRT, Intensity-Modulated Radiotherapy; PTV, planning target volume; OARs, organ-at-risks; ML, machine learning; CNN, convolution neural network; IP, inverse planning; PB-AIO, Protocol-based Automatic Iterative Optimization; MCO, multi-criteria or multi-objective optimization; KBP, Knowledge-based Planning; GAN, Generative adversarial network; FMCV, fluence map converted 3D volume; PFM, predicted energy flow diagram; HSE, Historical Suboptimal Set; MOAPN, multi-objective adjustment strategy network; RF, random forest; DM, digital macrograph; MTL, multi-task learning; GCN, graph convolutional network; MLC, multi-leaf collimator.

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Dose prediction

Dose prediction is mainly the dose distribution for PTV and OARs. Its generation can be seen as an iterative super-parametric adjustment process that achieves final balance by constantly balancing conflicting clinical goals [8]. Excellent dose prediction strikes a balance between PTV and surrounding OARs exposures: it minimizes OARs exposures while ensuring adequate PTV dosing [9]. At present, the generation of IMRT dose distribution widely used in clinical practice mainly depends on inverse planning (IP) [10]. Unlike the previous positive planning, IP allows physical therapists to preferentially determine the number and angle of irradiation fields, and the target doses of PTV and OARs, then provides the results to the computer, getting various parameters of the delivery plan finally. Although the proposal of this method reduces the work pressure of physicists to a certain extent, the total time consumption still cannot be underestimated. The introduction of dose prediction based AI has been demonstrated in many studies to free the physical therapist from the chore and improve the efficiency and quality of plan (See Fig. 1).

Traditional method

Hussein et al. [9] divided the automated planning methods (include dose prediction) applied in clinical practice since 2018 into three categories: Protocol-based Automatic Iterative Optimization (PB-AIO), multi-criteria or multi-objective optimization (MCO) [8,11–15], and Knowledge-based Planning (KBP). The PB-AIO and KBP have been separately commercialized and put into clinical practice: the Auto-Planning function of Pinnacle system [16–18], Rapid plan of Varian Eclipse TPS [9], MRIdian, Unity of Elekta, and Ethos of Vrian. KBP currently has more relevant studies.

According to the different methods used, KBP can be divided into two categories [19]: case-based and atlas-based methods, statistical modeling and machine learning methods. The core of the former mainly relies on the past similar cases, and transfer the useful knowledge from the plan to the current. The latter creates a predictive model based on clinical database. Regression model was mainly used in the past, but now traditional machine learning methods such as support vector machine and decision tree are also gradually used [19–25]. In 2014, Varian officially integrated the KBP-based DVH prediction model (named Rapid Plan) into its commercial development of TPS (Eclipse) and evaluated it well in multiple site tumors [19]. In recent years, with the advancement of online adaptive radiotherapy (oART), devices such as MRIdian, Unity, and Ethos can be used for oART treatment. MRIdian is based on the traditional Monte Carlo algorithm. Although it has high accuracy in calculation, it is limited by technical difficulties in the face of complex treatment plans (such as HNC). For example, the slow movement of MLC, the gantry rotation speed, limited beam Angle, etc [26]. Unity system and Ethos have high target coverage and OAR protection in terms of dosimetry, due to the necessity of clinicians to modify the target volume, the treatment time is longer than the traditional treatment method. Therefore, there is a tradeoff between the time spent adjusting the treatment plan and the dosimetric gain [27–29].

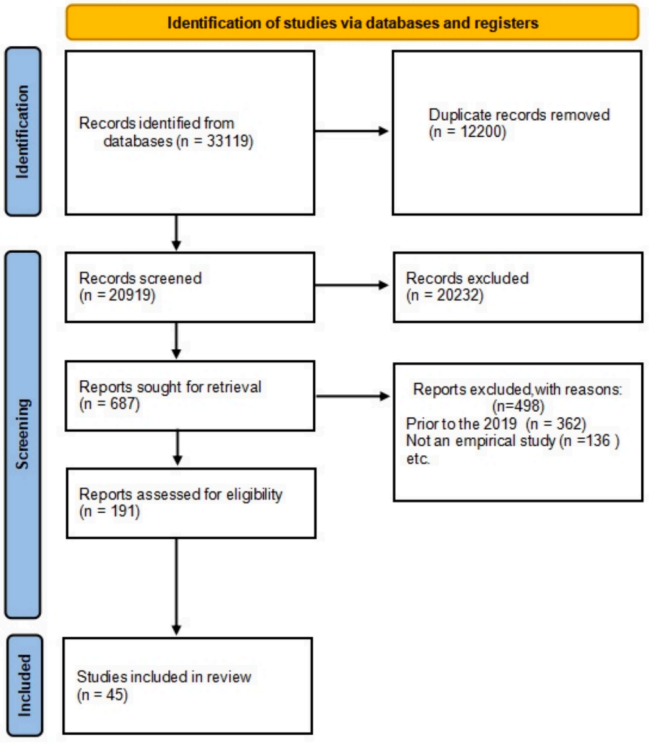

Fig. 1. Flow diagram of the search and selection process.

Although KBP has improved and accelerated the treatment process, it often limited by the quality of clinical treatment plan process. In addition, the predicted DVH curve lacks spatial information on dose distribution, which is inconsistent with the current overall goal of personalized and precise treatment [30–33].

Dose prediction based on deep learning

With the rapid development of DL, the focus of research has gradually tilted in recent years, and a large number of dose prediction models based on DL have been developed. Compared with the traditional machine learning method, DL can learn and acquire features from images without manual delineation. After acquiring each voxel information from patients' CT, MRI or PET, DL uses these information mapping to an optimal dose value, and then uses the voxel dose map to guide the optimization process in the TPS, and generate a final dose distribution [34]. In addition, the dose distribution can be predicted given the anatomical information and the dose prescription for use as a target for IP [35].

Dose prediction research related to DL gradually arose from 2012. Thanks to the increasingly mature application of CNN in radiotherapy, the proposal of the network optimized the defect of KBP in lack of three-dimensional information and retained the spatial relationship between each voxel. Now, it has been widely used in the field of dose prediction [34,36,37]. U-net, Generative adversarial network (GAN) and transformer are the main bodies of the current research [34].

U-Net

U-Net [35] is a convolutional network structure for fast and accurate volume segmentation. In dose prediction, it is able to collect local and global features from the input image to generate pixel or voxel predictions in its 2D or 3D variants, respectively.

In 2017, Nguyen et al. [38] first used the U-net in the dose prediction feasibility study, and developed a variant of the 3D U-Net model [39], i.e., the layered and densely connected U-net based on the U-Net and DenseNet [40], which shows that the model outperformed the other two models in terms of uniformity, dose consistency and dose coverage (single classical U-net and DenseNet).

Since Nguyen pioneered the U-Net variant, more and more studies have focused on the DL developed based on 3D U-Net. By changing the internal structure of the model, it can be combined with different ML methods, such as DenseNet [41], HD U-Net, DVHnet, and ResDevNet.Or by using various input data, such as distance information, PTV and OARs contour information, etc., with corresponding development in the fields of head and neck cancer [1,42–48], breast cancer [49,50], lung cancer [51,52], prostate cancer [36,44,53–59], and cervical cancer [60], respectively.

The superiority of dose prediction model lies not only in its structure,

but also in the input information. The input information can be divided into contour information, distance information, machine parameters, etc. In previous studies, the contour information was often used as a single input, while the Ma [55] additionally included dose distribution information that only considered PTV (i.e., a scheme that sacrificed OARs for optimal PTV coverage) to obtain more dose characteristics, thus helping to optimize dose distribution. Dong [61] established a Deep DoseNet model to collect missing density information from CT images to improve the resolution of the dose distribution. Fan [62] created fluence map converted 3D volume (FMCV), which directly used the fluence map as input to establish a direct mapping relationship with the 3D dose distribution, and proved its feasibility in different parts and had great potential to improve the calculation efficiency and accuracy. Peng et al. [63] directly extracted the 3D projections from the volume CT and anatomical data according to the beam incidence direction and used them as inputs to output the predicted energy flow diagram (PFM) of each beam. The PFM was then converted to an multi-leaf collimator (MLC) sequence with deliverable management to generate the final treatment plan.

Different from the data adjustment limited to the input, Hu et al. [64] made improvements to both input and output. They proposed the Historical Suboptimal Set (HSE: the set of multiple suboptimal models obtained in one round of training) for the first time. The non-intensity-modulated dose distribution (the initial amount conforming to the target shape during the IP) was used as input and HSE was used to improve the prediction accuracy. The experimental results showed that the non-intensity-modulated dose was faster than the conventional network, and it was more accurate for the prediction of quantitative indicators and high and low dose regions, and could reduce the deviation of the final prediction results.

Apart from the combination with traditional ML, emerging algorithms such as imaging omics and reinforcement learning (RL) are gradually applied to dose prediction. Lou, Doken et al. [65] have established a multi-task deep neural network —Deep Profiler, which combines neural network, imaging omics with clinical practice. By learning the multi-dimensional spatial characteristics of CT images of multiple patients receiving different doses of radiotherapy and connecting with imaging omics, these information and clinical variables are combined to obtain iGray, an individualized radiation dose. Wang et al. [66] included RL in CNN and developed a multi-objective adjustment strategy network (MOAPN) to learn how to adjust multiple objectives in TPS to achieve a high-quality plan (See Table 1).

GAN

GAN is learned through mutual game between two neural networks, which can enhance the robustness of the model. It is composed of two modules: a generation network and an discriminator network. The goal of the generation network is to generate data that simulate real samples in a training set as much as possible, while the discriminator network screens the output of the generation network from the real samples. These two networks achieve nash equilibrium through countermeasure training. However, the traditional GAN rely on the ability of the discriminator network to distinguish between false prediction and actual prediction, so the overall performance is limited by the authenticity ability of the identifier.

Due to the special ability of GAN to distinguish authenticity, the predicted dose closest to the clinical dose is often obtained clinically by developing GAN-based models. Aaron Babier et al. [67] constructed a 3D GAN model that can predict the dose of the entire 3D CT image at one time and consider the correlation between adjacent CT slices, thus meeting the criteria for clinical plan more than 3D Dosenet and 2D GAN. Subsequently, they [68] also performed a study on the synergistic performance of the dose prediction model and the optimization model, combining GAN and random forest (RF) with the optimization models IP and digital macrograph (DM), respectively, trained in oropharyngeal cancer patients and proved that the generated plan of GAN-IP was better than the other three, and that the performance of the automated KBP depended on the synergistic performance of the prediction and optimization model. Therefore, they suggest that multiple optimization models should be tested before the new prediction methods are considered to be state-of-the-art. Zhan et al. [69] proposed an automatic dose prediction framework Mc-GAN for multi-constrained GAN. In this model, it can learn the nonlinear mapping relationship between input (contour information) and output (dose distribution map), capture more local and global useful features to generate better results, avoid model over-fitting and improve the consistency between actual and predicted dose.

Most of the published studies use the manually sketched PTV and OARs contour information as the input to the model. Although accurate contour information can help to obtain a more true and accurate dose distribution, the time consumed in manually sketching may delay the treatment of the disease and lead to a poor prognosis. Murakami [70] and Cui et al. [71] attempted to develop a corresponding model based on GAN to predict dose distribution with only CT raw images as input, and verified their feasibility in prostate cancer and rectal cancer, respectively. The latter also introduced multi-task learning (MTL) strategy to compensate for missing anatomical information and demonstrated superior performance over other mainstream approaches (U-net, DeepLabV3+, DoseNet, and GAN) (See Table 2).

Transformer

Transformer is a neural network model based on self-attention mechanism, which is used to process sequential data. It adopts self-attention mechanism to capture the correlations within a sequence and overcome the limitations of long-range dependencies. By parallelizing the training process, the training speed can be improved [74]. Currently, it has been applied in various domains such as image classification, target detection, and semantic segmentation, etc. Due to the lack of global feature acquisition in CNN, researchers have employed the transformer and developed several superior dose prediction models in combination with other DL models [74–81]. Wen et al. [80] argue that existing DL models overlook the isodose lines and gradient information in dose maps. They embed the Transformer to address the lack of global features and establish the TransMTDP multi-task dose prediction network, which has been validated to be superior in rectal cancer and head and neck cancer datasets. Jiao et al. [76] firstly utilized a graph convolutional network (GCN) based on superpixels to extract anatomically relevant features and embed the Transformer into the backbone network, establishing the TransDose model. This model solely employs CT images for dose prediction and has demonstrated its generalization ability and superiority through extensive experiments (See Table 3).

Considering the individual differences of patients, the parameters of the treatment machine will not be static when treatment is delivered, and the accurate dose distribution is not only predicted based on the individual information of patients. The unsatisfactory delivery parameters such as the shape, angle, beam direction, and medium density of the MLC can also lead to large deviation between the treatment dose and the planned dose. Thus, direct machine parameter prediction is another potential area of study in which the optimization of a plan as well as its deliverability can be considered based on the precision of the planned dose [52,58,74,78,82–84]. Kontaxis et al. [85] established the DeepDose framework for accurate dose calculation of IMRT MLC shapes, which utilized different anatomical structures and patient anatomy as inputs to predict the dose for each individual part of the patient's plan based on the actual machine parameters of the linear accelerator. Gyanendra [58] and Ana et al. [52] used given set of beam angles and patient anatomy as model inputs, adding the ability to adjust beam orientation to the Pareto optimal dose prediction model based on DL without the need to train specific models for each beam arrangement.

Based on the dose prediction studies, some studies has been realized the direct automation of treatment planning. Fan et al. [45] designed an automatic voxel-based planning method based on matRad [86]: using CT images and outlining information as inputs, and integrating dose

Table 1
Selected studies on Unet-based dose prediction.

Reference and years	Dataset	Model	Input	Output	Main results
Chen et al [42]/2021	Nasopharyngeal cancer:180 Training set:153 Testing set:27	DVHnet	Two-channel images with contoured structures.	DVH curve for each slice.	Mean difference of all OARs: 0.30 ± 0.95 Gy Differences in D2% and D50: within 2.32 and 0.69 Gy.
Fan. et al [45]/2019	H&N cancer:270 Training set:195 Validation set:25 Testing set:50	Residual neural network	The image representing the patient anatomy in each trans-axial CT slice.	Dose distribution.	Except brainstem, right and left lens, there is no statistically significant difference between prediction and real clinical plan.
Chen. et al [46]/2018	Early-stage nasopharyngeal cancer (NPC):80 Training set:70 Test set:10	ResNet101	Two inputs: one included the images (with associated structures) without manipulation; another involved modifying the image gray label with information from radiation beam geometry.	Dose distribution.	Using radiation geometry performed better than another.
Fan et al [62]/2021	Nasopharyngeal, lung, rectum and breast cancer:267 Training set:200 Validation set:20 Test set:47	Voxel traversal algorithm	Each individual beam	Dose distribution	The average per-voxel bias and standard deviation:0.17 % ± 2.28 %.
Ma et al. [44]/2022	Head and Neck cancer:443; Prostate cancer:14 Training set:457 Validation set: 49 Test set:102	DNN (U-net)	Desired volumetric dose distribution	Ground truth (GT)	The mean dose difference (PTV):1.42 %±0.37 %
Xing et al [36]/2020	Lung cancer:120 Training set:72 Validation set:18 Testing set:30	HD U-Net	The fluence map and CT	Dose distribution	New model average gamma passing rate:97.6 %(±2.4 %),old:87.8 % (±9.0 %) MSE:0.11(±0.05)vs 0.31(±0.21).
Montero et al [52]/2019	Lung cancer:129 Training/validation set:100 Testing set:29	Hierarchically densely connected U-Net (HD U-net)	10 input channels: one for beam setup and the other 9 for anatomical information (PTV and organs).	Dose distribution	Dice scores: in low and medium dose region: AB model 10 % higher than the AO model; high:2–5 %
Ahn et al [49]/2021	Breast cancer:55 Training set:35 Testing set:10 Validation set:10	DpNet	CT images	Dose distribution	MAE ± SD between clinical and DpNet:$D_{95\%}$ 0.02 ± 0.04 %,D_{mean} 0.01 ± 0.83 %.
Xing et al [36]/2020	Prostate cancer:78 Training set & validation set:70 Testing set:8	A modified Hierarchically Densely Connected U-net (HD U-net)model	Pre-calculated inaccurate dose distribution and patient CT	Dose distribution	The dose difference between DL and CS < 0.25 Gy;for volume:<0.16 %.
Ma et al [43]/2021	Prostate cancer:97 Training/Validation set:77 Testing set:20	3D U-net	Patient PTV/OAR masks and the desired DVH.	Dose distribution	The largest average error: mean dose 1.6 %,maximum dose 1.8 %
Ma et al [53]/2019	Prostate cancer:70 Training set:60 Test set:10	CNN	The contours of six structures in CT images	Dose distribution	Mean SARs:0.029 ± 0.020 (bladder),0.077 ± 0.030(rectum).
Kandalan et al[54]/ 2020	Prostate cancer:248 Training set:108 Test set:14–29	3D U-Net; transfer learning	The contours of PTV and the OARs;	Dose distribution	With transfer learning, the model can improved the mean DSC to 0.88–0.95 and 0.92–0.96 for internal and external styles.
Ma et al [55]/2019	Prostate cancer:70 Training set:60 Test set:10	CNN	Contour information and the dose distribution from a PTV-only plan	Dose distribution	The mean SARs:PTV 0.007 ± 0.003, bladder 0.035 ± 0.032, rectum 0.067 ± 0.037.
Sumida et al [56]/2020	Prostate cancer:66 Training &validation set:50 Testing set:16	U-net	The CT images	Dose distribution	The mean DSC: DC model 0.763,D model 0.592.
Kajikawa et al[57]/ 2019	Prostate cancer:95 Training &validation set:80 Test set:15	CNN (3D U-net)	The contours for PTVs and OARs	Dose distribution	MAE with ISD between clinical and CNN:D2 1.10 %±0.64 %.
Bohara et al [58]/2020	Prostate cancer:70 Training set:54 Validation set:6 Test set:10	U-Net	Model I:converting the PTV,OARs and body into beam angles Model II: converting the beam angles into beam doses	Dose distribution	Model I's prediction error:0.327 (R50), 3.90 % (D98);Model II:0.626 (R50), 6.50 % (D98).
Ni et al[59]/ 2022	Prostate cancer:171 Training set:144 Testing set:27	3D U-Net	Patients' CT and contour information	Dose distribution	$V_{95\%}$ > 99 %, $V_{107\%}$<0.2 %.

(*continued on next page*)

Table 1 (*continued*)

Reference and years	Dataset	Model	Input	Output	Main results
Kearneyet al [41]/2018	Prostate cancer:151 Training set:106 Validation set:20 Test set:25	DoseNet	3D CT, prostate, bladder, penile bulb, urethra, and rectum volumes.	Dose distribution	Average ΔDoseNet: CI (conformity index) 0.04,HI (heterogeneity index) 0.03.
Dong et al [61]/2021	Ten patient CT image datasets of different disease sites	DDN (Deep Dose Net)	The AAA dose slices, and the corresponding down sampled CT slices	Dose distribution	The average mean-square-error between DDN and AXB:7.0 × 10^ [-5].
Zhang et al [60]/2020	Cervical cancer:100 Endometrial cancer:20 Training set:86 Validation set: 11 Test set:20	3D U-Net	Contoured structures	Dose distribution	The average DSCs under different isodose volumes > 0.9.
Peng et al [63]/2023	Rectal adenocarcinoma:334 Training & validation set:314 Test set:20	CNN;3D residual U-Net	Projections in cone beam space	Predicted fluence map (PFM)	Compared to manual plans, RTTP increases in PTV D1% by 2.33 % ($p < 0.001$), a decrease in PTV D99% by 0.45 % ($p < 0.05$).
Hu et al[64]/ 2020	GO disease:107 Training set:76 Validation set:13 Test set:18	DNN	The nonmodulated dose distribution	Dose distribution	PTV D99:92.533 ± 83.757, HI 0.041 ± 0.046,CI 0.091 ± 0.102.

Table 2
Selected studies on GAN-based dose prediction.

Reference and years	Dataset	Model	Input	Output	Main results
Babier et al[67]/ 2019	Oropharyngeal cancer:217	3D GAN	Contoured CT images	Dose distribution	3D GAN satisfied 77 % of all clinical criteria, clinical plan satisfied 67 %.
Babier et al[68]/ 2020	Oropharyngeal cancer:217 Training set:130 Test set:87	Two dose prediction method: GAN,RF. Two optimization models: IP, DM	Contoured CT image	Dose distribution	GAN-IP satisfied 78 % clinical criteria; GAN mean absolute error:3.9 Gy.
Zhan et al[69]/ 2022	Cervical cancer:42 Rectal cancer:130 Training set:136 Validation set:7 Testing set:29	Mc-GAN: composed by EmbUNet, AdvNet, SENet,	The original CT, the mask of PTV and OARs	Dose distribution	In cervical cancer: PTV D_{98} 0.007 ± 0.004,D_2 0.002 ± 0.001,HI 0.007 ± 0.006,CI 0.020 ± 0.012.In rectal cancer: PTV D98 0.008 ± 0.006,D2 0.006 ± 0.004,HI 0.012 ± 0.005,CI 0.013 ± 0.008.
Murakaml et al [72]/2020	Prostate cancer:90 Training set:81 Test set:9	GAN	Paired CT images	Dose distribution	The mean difference of OARs were within approximately 2 % and 3 %(except for $D_{98\%}$, $D_{95\%}$ for PTV)
Cui et al[71]/ 2022	Rectal cancer:130	GAN with multi-task learning (MTL) strategy	CT images only	Dose distribution	HI:1.023, ΔD_{95}:0.125, ΔD_{mean}:0.023
Li et al[73]/2021	Oropharyngeal cancer:231 Training set:200 Validation set:16 Test set:15	cGAN-Conditional generative adversarial network.	3D CT volume and structures	Fluence map	D_{mean} of left parotid: 23.1 ± 2.4 Gy, D_{mean} of right parotid: 23.8 ± 3.0 Gy, D_{max} at 0.01 cc of brainstem: 15.0 ± 2.1 Gy, D_{max} of body: 121.1 ± 3.9 Gy.

prediction and reverse optimization in the same process, without human participation in the whole process. Liu et al. [73] developed a GAN-based AI proxy model, which can directly generate the optimal ray flux intensity map of IMRT when being trained in patients with nasopharyngeal carcinoma, and no reverse planning or dose prediction is required in the process. The generated flux map can be converted directly into a deliverable plan in the business process planning system.

Discussion

Dose calculation is a vital part of RT, which is a time-consuming and labor-intensive process. Especially with the increasing attention paid to individualized treatment and precise radiotherapy, it's challenged to consider the patient-specific and achieve the optimal dose distribution at the same time. It not only requires accurate dose calculation, but needs to select the matching treatment parameters. The whole formulation process is complex and endless. The emergence of dose prediction models will help to improve this situation.

Recent years, with the rapid development of AI, it has been successfully applied in various fields of society and life, such as defeating the world champion of alphago, and autonomous vehicle. Its achievements in the medical field are also brilliant, mainly in medical imaging, auxiliary diagnosis, drug research and development, health management, and disease prediction. In the field of medical imaging, although AI is still in the trial stage, mature products have been produced in such fields as tuberculosis, fundus, breast cancer, and cervical cancer [87]. Based on these successful cases, AI has been gradually combined with RT. At present, mature commercial software has been put into use in image fusion and registration, target delineation, dose prediction, quality assurance, toxicity prediction, and other links.

The early researches of AI in dose prediction mainly focused on traditional ML methods such as regression analysis, support vector machine, and decision tree. With the deepening of research on DL, ML has a more comprehensive application prospect, which can process larger database and obtain more detailed features for training models, improve model prediction performance, and maximize the realization of

Table 3
Selected studies on transformer-based dose prediction.

Reference and years	Dataset	Model	Input	Output	Main results
Yang et al[74]/ 2022	Brain tumor:120 Training set:80 Validation set:20 Test set:20	TS-Net	A CT image, a PTV image, an OARs image, a beam configuration image, and a distance image	Dose distribution	MAE:2.98 % for PTV. For most isodose volumes,DSC > 0.91.
Yue et al[75]/ 2022	Nasopharyngeal carcinoma:161 Training set:130 Validation set:11 Test set:20	3D U-Net	Distance map	Dose map	The predicted dose error and DVH error are 7.51 % and 11.6 % lower than the mask-based method
Jiao et al [76]/ 2023	Rectal cancer:120 Cervical cancer:42 Training set:116 Validation set:12 Testing set:34	Super-pixel-level GCN	CT images	Dose map	HI 0.352;ΔD_{95} 0.150; ΔD_{mean} 2.40E-2; ΔD_{max} 1.68E-2
Pastor-Serrano et al[77]/ 2022	Training set:17 with disease sites of brain, head neck, lung, abdomen and pelvis Validation set:10 % of training set's CT slices Test set:584 beam dose distributions	iDoTA	CT images	Dose distribution	Gamma pass rate in 50 ms:97.72 ± 1.93 %. Pass rate in 6–12 s:99.51 ± 0.66 %, average relative dose error:0.75 ± 0.36 %.
Hu et al[78]/ 2023	Head and neck cancer:340 Training set:200 Validation set:40 Test set:100	TrDosePred	Contoured CT image	Dose distribution	MAE against the clinical plan:2.25 %for targets,2.17 %for organs at risk
Zeng et al[79]/ 2023	Under VMAT:307 Training set:246 Test set:61	TransQA	CT images	Predicted high-quality voxel-wise prePSQA dose distribution	SSIM:0.9944 % MAE:0.2514 % RMSE:0.7468 %
Wen et al[80]/ 2023	Rectum cancer:110 H&N cancer:340 Training set:88 + 270 Test set:22 + 70	TransMTDP	CT images, the PTV,OAR segmentation masks	Dose distribution maps, isodose lines maps, gradient maps	Rectum cancer: HI 0.856,D_{max} 54.03,D_{mean} 50.86 H&N cancer: HI 0.101 D_{max} 67.43 D_{mean} 33.30
Cui et al[81]/ 2023	Rectal cancer & cervical cancer:120,42 Training set:120 + 28 Validation set:2 Test set:12	A DAEncoder and two CNNs-based domain decoders	CT images and the organ segmentation masks	Dose distribution	ΔD_{98}:1.446 ΔD_{95}:1.231 HI:0.082

individualized precision radiotherapy. In conclusion, compared to conventional methos, AI can be used to achieve the optimal dose distribution in patients, evaluate the individualized treatment effect, and propose the dose distribution scheme for reference and improvement by clinicians and physicists. At the same time, it can tremendously reduce the time and labor cost on the basis of ensuring the dose accuracy, freeing clinicians and physicians from the procedure of dose calculation and focusing more energy on other procedures of radiotherapy, such as target delineation, which may reduce the waiting time of patients for treatment, improve treatment efficiency, thus improve the prognosis of patients.

Despite the successful use of AI in dose prediction, certain aspects remain problematic. Firstly, in terms of data, small data sets is a common problem in most studies. Model training, validation, and testing rely on a large and high-quality database. Studies have shown that the quality and scale of data have a direct impact on model performance [34]. The training data and validation data should be separated from the test data for rigorous model training and testing. If there is no enough data for model training and testing, the overly complex model generated from the limited dataset will often be over-fitted, which will affect the generalization performance of the model. Therefore, it is essential that large data sets be of high quality and publicly available. However, it is not easy for a single tumor center to acquire large enough data sets. If multi-center database cooperation is realized, it may be possible to solve this problem. Image-net algorithm has also been proven to be effective. Ethically, due to the structure and operation principle of AI, especially DL, are not transparent, and even researchers cannot explain its operation principle in detail, it is called a "black box", and its availability and authenticity are often questioned by the outside world, so a comprehensive, thorough and strict quality assurance link is needed to ensure the high safety of clinical practice in generating plans. In terms of clinical application, relevant studies have proved that the algorithm of dose prediction, automation increasing error probability, and clinical workers' concern for the safety of automation are the main obstacles to its successful clinical application [88]. In addition, except for a few studies [89], the current model generalization is limited by data, machines, and researchers' experience and consensus. Most of the developed models are confined to the same treatment center and do not have the ability to be widely used. In terms of efficiency, the recent research also reminds us that although researchers develop excellent models as much as possible to efficiently generate the optimal dose distribution, most models use contour information as input, that is, PTV and OARs, and this step needs accurate delineation results [71,72]. A mature radiotherapy doctor needs at least three hours to complete this process. Even if AI is included, artificial calibration still needs a lot of time. Therefore, the time required for obtaining a truly accurate dose distribution may be much longer than expected. Finally, there is a lack of consensus on defining criteria that objectively judge whether a clinically acceptable "best" treatment is acceptable. Researchers usually compare various quality indicators with manual plans, and often calculate the loss function based on the mean absolute error of voxels, 3D gamma analysis of global or local structure, and so on. There is a lack of uniform high-quality indicators for evaluation, resulting in the lack of objectivity in most studies.

Although the problems of AI in dose prediction cannot be ignored, its advantages of high efficiency, high consistency, high precision rate of shoulder-to-shoulder clinical dose prediction, and fully liberating labor force make clinical work benefit a lot. I believe that its deficiencies will

be effectively resolved in the near future.

Conclusions

This paper reviews the application and research progress of AI in dose prediction, and probes into the problems existing in the current research. AI greatly shortens the time of radiotherapy dose prediction and plan formulation, and has a greater breakthrough in accuracy and feasibility, thereby not only avoiding uneven treatment effects caused by experience differences of medical centers or medical workers, but also streamlining the whole workflow for RT, enabling patients to benefit from the results. However, various existing problems will directly affect the possibility of its clinical application, and still need to be properly resolved in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

C.J. designed and drafted the manuscript, performed literature research and data extraction. T.J. reviewed the manuscript. Q.Q.: designed and supervised the study. All authors read and approved the final manuscript.

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Not applicable.

Appendix A. Supplementary data

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