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RADIOTHERAPY

Artificial intelligence applied to image-guided radiation therapy (IGRT): a systematic review by the Young Group of the Italian Association of Radiotherapy and Clinical Oncology (yAIRO)

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Abstract

Introduction The advent of image-guided radiation therapy (IGRT) has recently changed the workflow of radiation treatments by ensuring highly collimated treatments. Artificial intelligence (AI) and radiomics are tools that have shown promising results for diagnosis, treatment optimization and outcome prediction. This review aims to assess the impact of AI and radiomics on modern IGRT modalities in RT.

Methods A PubMed/MEDLINE and Embase systematic review was conducted to investigate the impact of radiomics and AI to modern IGRT modalities. The search strategy was "Radiomics" AND "Cone Beam Computed Tomography"; "Radiomics" AND "Magnetic Resonance guided Radiotherapy"; "Radiomics" AND "on board Magnetic Resonance Radiotherapy"; "Artificial Intelligence" AND "Cone Beam Computed Tomography"; "Artificial Intelligence" AND "Magnetic Resonance guided Radiotherapy"; "Artificial Intelligence" AND "on board Magnetic Resonance Radiotherapy" and only original articles up to 01.11.2022 were considered.

Results A total of 402 studies were obtained using the previously mentioned search strategy on PubMed and Embase. The analysis was performed on a total of 84 papers obtained following the complete selection process. Radiomics application to IGRT was analyzed in 23 papers, while a total 61 papers were focused on the impact of AI on IGRT techniques.

Discussion AI and radiomics seem to significantly impact IGRT in all the phases of RT workflow, even if the evidence in the literature is based on retrospective data. Further studies are needed to confirm these tools' potential and provide a stronger correlation with clinical outcomes and gold-standard treatment strategies.

Keywords Artificial intelligence · Radiomics · Deep learning · Machine learning · Image-guided radiation therapy

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Introduction

Artificial intelligence (AI) is a field of computer science capable of analyzing complex datasets and exploring meaningful relationships within different data formats. It has been applied in numerous health care settings, such as diagnosis, treatment optimization and outcome prediction [1].

AI is based on a wide collection of algorithms to perform tasks correlated with human thinking or intelligence through the appliance of machine learning (ML) and deep learning (DL) as subdomains [2].

The applications of AI in radiotherapy (RT) are numerous and aim to improve the accuracy, precision, efficiency and overall quality of the treatment of cancer patients [3, 4].

Automated segmentation, automated planning, synthetic image generation and automated quality assurance represent only some of the applications of AI in RT, opening new frontiers in several steps of the RT workflow [5–7].

AI has been successfully applied also to image sciences. As an example, radiomics can provide quantitative features from medical images that can be correlated with various biological characteristics and clinical endpoints [8]. Its use in the field of radiation oncology has offered new important insights for treatment optimization [8–12].

Radiomics allows researchers to predict different outcomes (i.e., response to treatment or treatment-induced toxicities) and can be applied also to RT treatment-related images, besides the traditional applications to standard diagnostic images [13–16].

Image-guided Radiation Therapy (IGRT) has become increasingly important in recent years, allowing to overcome numerous pitfalls of past RT. Indeed, IGRT is crucial in highly conformal treatments made possible by the recent volumetric techniques such as intensity-modulated Radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) [17, 18].

IGRT allows to verify the correct position of the target and the inter-fraction and intra-fraction variability of the therapy volumes, reducing the risk of target missing and unnecessary irradiation of organs at risk (OAR) that may cause potentially severe treatment-related toxicity, especially in high-dose single fraction treatments such as stereotactic body RT (SBRT) [19, 20].

The recent introduction of Magnetic Resonance imaging-guided radiotherapy (MRIgRT) has brought further innovations, thanks to the new application of AI techniques, such as the possibility to perform active direct gating on movable targets and online treatment adaptation [21].

AI can facilitate and speed up these processes, especially in online adaptive radiotherapy treatments (ART) [22–24].

These new techniques are supporting the introduction of innovative treatment regimens that may obtain more effective and safe treatments for cancer patients [25–29].

This will pave the way towards more hypofractionated regimens, escalating treatment doses, and reducing hospital access and relative logistic burden, as recently observed also during the Covid19 pandemic [30].

The aim of this systematic review is to assess the status and future perspectives of the use of AI and Radiomics applied to images applied in-room through IGRT technologies.

Materials and methods

A PubMed/MEDLINE and Embase systematic search was performed using definite keywords, according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [31].

The searching strategy included the following keywords: (“Radiomics” [Mesh] OR “Radiomics” [All fields]) AND (“Cone Beam Computed Tomography” [Mesh] OR “Cone Beam Computed Tomography” [All fields]); (“Radiomics” [Mesh] OR “Radiomics” [All fields]) AND (“Magnetic Resonance guided Radiotherapy” [Mesh] OR “Magnetic Resonance guided Radiotherapy” [All fields]); (“Radiomics” [Mesh] OR “Radiomics” [All fields]) AND (“on board Magnetic Resonance Radiotherapy” [Mesh] OR “on board Magnetic Resonance Radiotherapy” [All fields]); (“Artificial Intelligence” [Mesh] OR “Artificial Intelligence” [All fields]) AND (“Cone Beam Computed Tomography” [Mesh] OR “Cone Beam Computed Tomography” [All fields]); (“Artificial Intelligence” [Mesh] OR “Artificial Intelligence” [All fields]) AND (“Magnetic Resonance guided Radiotherapy” [Mesh] OR “Magnetic Resonance guided Radiotherapy” [All fields]); (“Artificial Intelligence” [Mesh] OR “Artificial Intelligence” [All fields]) AND (“on board Magnetic Resonance Radiotherapy” [Mesh] OR “on board Magnetic Resonance Radiotherapy” [All fields]).

Original articles up to 01.11.2022 were selected, and the exclusion criteria were defined as: 1) not original articles (e.g., abstracts, reviews, editorials, book chapters, letters, congress communications or posters); 2) articles that were not in English language; 3) papers not referred to IGRT imaging techniques; 4) papers not presenting results about radiomics and AI applications.

A board composed by two radiation oncologists (AD, AP) selected all articles, an independent validation of three experts in radiomics and AI was also performed (LB, VN, VS).

A final validation of the whole process was performed by other 5 different independent expert radiation oncologists (FDF, ID, RG, CG, GCI).

Results

A total of 402 studies were obtained using the mentioned search strategy on PubMed/MEDLINE and further 249 articles were obtained on EMBASE.

Following title and abstract analysis, 131 papers were selected according to the previously reported exclusion criteria.

After full-text analysis, 44 papers were discarded according to selection criterion 4, as not referred to radiomics or AI applied to IGRT imaging modalities. After the completion of the selection process, 84 papers were considered eligible for the analysis of the results.

Figure 1 reports the flowchart of the systematic literature search process.

The range of publication year goes from 2011 to 2022 and all the studies included in the analysis resulted to be retrospective.

In the subset of papers regarding radiomics ($n=23$), the feature extraction was performed on on-board MR treatment images in 31% ($n=7$) [9, 11, 14, 32–35] and CBCT in 69% ($n=16$) of the cases [36–51]. The median number of patients involved in the analysis was 30 (range 10–337); the median number of considered radiomics features was 110 (range 2–2317).

Eight studies (34%) analyzed the technical feasibility and reproducibility aspects of radiomics analysis [11, 14, 32–34, 36–44], while the correlation of radiomic features and treatment response was the focus of fifteen studies (66%) [35, 45–51].

Table 1 summarizes the main characteristics of the analyzed radiomics studies, including aim, conclusions, and corresponding cluster area.

In the subset of papers regarding AI ($n=61$), the analysis was performed on CBCT in the 56% ($n=34$) [52–87] and on MRIgRT treatment images in the 44% ($n=27$) [5, 52, 79, 88–111].

The median number of patients involved in the analysis was 45 (range 1–480).

Thirty studies (49%) analyzed AI in the generation of synthetic imaging [5, 52–70, 75, 79, 88–93, 99], while autosegmentation and autoplanning were investigated in 20 studies (32%) [71–79, 95–106]. Plan quality assurance and dose calculation were the focus of 15 papers (24%) [55, 57–59, 63–65, 67, 69, 70, 80, 81, 94, 107, 108], treatment delivery optimization was investigated in eight studies (12%) [82–86, 90, 109, 110], while response prediction in 2 studies (3%) [87, 111] as summarized in Tables 2 and 3.

Discussion

The results of this systematic review underline the effort that the radiation oncology community has addressed to apply radiomics and AI modalities on modern IGRT images as a result of the ongoing attempts to provide personalized radiotherapy treatment and workflow optimizations.

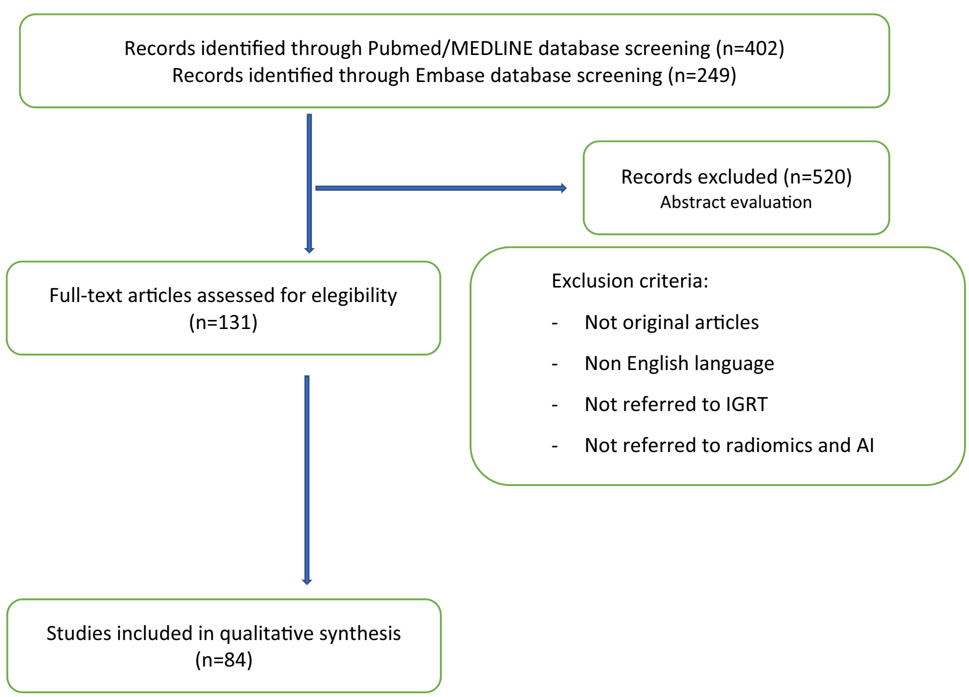

Fig. 1 Flowchart of the systematic literature search process

Table 1 Articles regarding radiomics applied to in-room IGRT images

First author (country/year)		No of patients	Objectives	Cluster area	IGRT modality	No of features	Conclusions
Boldrini L et al. (Italy, 2019)	[14]	16	To predict cCR in patients affected by RC undergoing neoadjuvant CRT using 0.35 T MRI-based delta-radiomics features	Treatment response prediction	MRgRT	318	0.35 T MRI-based delta-radiomics is promising to predict cCR (p value < 0.001)
Tomaszewski M R et al. (USA, 2021)	[32]	26	To predict PFS in patients affected by PDAC undergoing SBRT using 0.35 T MRI-based delta-radiomics features	Treatment response prediction	MRgRT	73	0.35 T MRI-based delta-radiomics is promising to predict PFS prediction (p value = 0.005)
Chiloiro G et al. (Italy, 2022)	[33]	48	To predict 2yDFS in patients affected by RC undergoing neoadjuvant CRT using 0.35 T MRI-based delta-radiomics features	Treatment response prediction	MRgRT	1099	0.35 T MRI-based delta-radiomics is adequate to predict DFS (AUC 0.92)
Simpson et al. (USA,2022)	[34]	30	To predict treatment response in patients with PDAC who underwent SBRT using 0.35 T MRI-based delta-radiomics	Treatment response prediction	MRgRT	39	0.35 T MRI-based delta-radiomics is adequate to predict tumor response (AUC 0.845)
Xue C et al. (China, 2021)	[35]	26	To determine repeatability of radiomics features between MR-LINAC scans and reproducibility between MRI-simulator and MR-Linac scans	technical feasibility and reproducibility aspects of radiomics analysis	MRgRT	1023	A reliable selection of MRgRT features is needed for the validation of radiomics studies
van Timmeren J A et al. (the Netherlands, 2019)	[36]	337	To predict toxicity and OS and LC in lung cancer patients undergoing CBCT-based RT. Validation of longitudinal methods	Treatment response prediction	CBCT pCT	2317	No validation of clinical parameters for OS and LC
Qin Q et al. (China, 2021)	[37]	34	To predict toxicity and PFS in lung cancer patients undergoing CBCT-based SBRT	Treatment response prediction	CBCT	144	CBCT-based radiomics resulted to be adequate in predicting PFS (AUC 0.918) and lung injury (AUC 0.952)
Bosetti D G et al. (Switzerland, 2020)	[38]	31	To predict risk stratification and biochemical relapse in PC patients undergoing CBCT-based RT	Treatment response prediction	CBCT	31	CBCT-based radiomics is adequate to predict selected outcomes (AUC 0.83–0.93)
Shi L et al. (USA, 2020)	[39]	23	To predict OS in locally advanced in lung cancer patients undergoing CBCT-based RT	Treatment response prediction	CBCT	658	Early CBCT-based radiomics features could be correlated with overall survival in locally advanced lung cancer (p value < 0.05)

Table 1 (continued)

First author (country/year)		No of patients	Objectives	Cluster area	IGRT modality	No of features	Conclusions
Morgan H E et al. (USA, 2021)	[40]	30	To predict LF in H&N patients undergoing CBCT-based RT	Treatment response prediction	CBCT	30	CBCT-based radiomics resulted to be adequate in predicting LF in primary (AUC 0.871) and nodal (AUC 0.91) sites
Du F et al. (China, 2020)	[41]	96	To develop a nomogram predicting the risk of RT related pneumonitis in esophageal squamous cell carcinoma	Treatment response prediction	CBCT	851	CBCT radiomics provided a model based on early lung CBCT for predicting pneumonitis (AUC 0.836–0.918)
Sellami S et al. (France, 2022)	[42]	93	To identify a CBCT radiomic signature predictive of progression in H&N radiotherapy	Treatment response prediction	CBCT	88	The CBCT radiomics model showed an early change in features possibly correlating with treatment response
Iliadou V et al. (Greece, 2022)	[43]	40	To develop a CBCT radiomics-based model to determine tumor volume variations in H&N radiotherapy	Treatment response prediction	CBCT	104	CBCT features analysis led to a high accuracy (0.90 $p < 0.01$) in determine CTV variations
Zhang R et al. (China, 2022)	[44]	10	To develop a CBCT radiomics-based model to determine tumor volume variations in lung radiotherapy	Treatment response prediction	CBCT	1371	CBCT analysis led to the identification of stable radiomics features to predict tumor response during RT
van Timmeren J A et al. (the Netherlands, 2017)	[45]	90	To determine a selection model for radiomics features in lung cancer patients undergoing CBCT-based RT	technical feasibility and reproducibility aspects of radiomics analysis	CBCT	116	Combining baseline and longitudinal radiomics resulted in a reliable selection model in LC
van Timmeren J A et al. (the Netherlands, 2017)	[46]	288	To investigate the interchangeability of pCT and CBCT extracted radiomic features to predict survival in lung cancer patients undergoing CBCT-based RT	technical feasibility and reproducibility aspects of radiomics analysis	CBCT pCT	1119	CBCT radiomics can provide selected features that are interchangeable when extracted from either planning CT or cone-beam CT images
Delgadillo R et al. (USA, 2021)	[47]	20	To determine repeatability of radiomics features in PC RT	technical feasibility and reproducibility aspects of radiomics analysis	CBCT pCT	42	CBCT radiomic features showed correlation with pCT features also to be used for prognostic models
Bagher-Ebadian H et al. (USA, 2017)	[48]	18	To investigate the characteristics of radiomics feature in CBCT and pCT images in H&N radiotherapy	technical feasibility and reproducibility aspects of radiomics analysis	CBCT pCT	165	CBCT and pCT radiomics features showed interchangeability investigating radiomics features as possible biomarkers for outcome

Table 1 (continued)

First author (country/year)		No of patients	Objectives	Cluster area	IGRT modality	No of features	Conclusions
Fave X et al. (USA, 2015)	[49]	10	To determine the feasibility of CBCT-based radiomics features analysis in lung cancer radiotherapy	technical feasibility and reproducibility aspects of radiomics analysis	CBCT	68	CBCT radiomics features were found to be consistent in image protocols with less than 1 cm of tumor motion
Wang H et al. (China, 2021)	[50]	20	To determine the repeatability and reproducibility of CBCT radiomics features in H&N and pelvic radiotherapy	technical feasibility and reproducibility aspects of radiomics analysis	CBCT	18	CBCT radiomics features were found to both repeatable and reproducible even if disease/protocol-specific and correlated to time between scans
Gu J et al. (China, 2018)	[51]	22	To determine reproducibility of MVCT images radiomics analysis in lung cancer tomotherapy	technical feasibility and reproducibility aspects of radiomics analysis	CBCT	195	MVCT features analysis resulted to be feasible even if motion frequency could affect texture features
Cusumano D et al. (Italy, 2021)	[11]	43	To validate a prediction model for cCR and pCR in patients affected by RC undergoing neoadjuvant CRT using 0.35 T MRI-based delta-radiomics features	Treatment response prediction	MRgRT	2	0.35 T MRI-based delta-radiomics is adequate to predict cCR and pCR (AUC 0.81)
Cusumano D et al. (Italy,2021)	[9]	35	To predict LC in patients affected by PDAC undergoing SBRT using 0.35 T MRI-based delta-radiomics features	Treatment response prediction	MRgRT	92	0.35 T MRI-based delta-radiomics is promising in 1-year local control prediction (AUC = 0.78, p value = 0.005)

Table 2 Articles regarding AI applied to CBCT IGRT

First author (country/year)		No of patients	Objectives	Cluster area	IGRT modality	Conclusions
Scholey J E et al. (USA, 2022)	[52]	120	To implement an MR-only workflow by synthesizing MVCT from MRI	Synthetic imaging generation	CBCT MRgRT	The study demonstrates the feasibility of using MRI-derived sMVCT in an MR-only treatment planning workflow
Liang X et al. (USA, 2019)	[53]	110	To develop a DL approach to generate sCT images from CBCT in H&N RT	Synthetic imaging generation	CBCT	The study demonstrated the feasibility of sCT generation using generative adversarial networks
Yuan N et al. (China, 2020)	[54]	55	To develop a DL model to enhance CBCT images for adaptive H&N radiotherapy	Synthetic imaging generation	CBCT	The study demonstrated the quantitative and qualitative accuracy of DL generated CBCT images
Irmak S et al. (Austria, 2021)	[55]	41	To develop a DL approach to generate sCT images from CBCT mages in H&N RT	Synthetic imaging generation Plan quality assurance and dose calculation	CBCT	The study demonstrated the feasibility of sCT generation using a DL approach with good dose calculation results (gamma pass rates $99.0 \pm 0.4\%$)
Chen L et al. (USA, 2021)	[56]	143	To develop a DL approach to generate sCT images from CBCT mages	Synthetic imaging generation	CBCT	The study demonstrated the effectiveness of sCT generation using a DL approach
Gao L et al. (China, 2021)	[57]	170	To develop attention-guided generative adversarial networks approach to generate sCT images from CBCT	Synthetic imaging generation Plan quality assurance and dose calculation	CBCT	The study demonstrated the feasibility of sCT generation using a DL approach with good dose calculation results (gamma pass rates (91.4 ± 3.26)
Qiu R L J et al. (USA, 2021)	[58]	20	To develop DL to generate sCT images from thoracic SBRT CBCT	Synthetic imaging generation Plan quality assurance and dose calculation	CBCT	The study demonstrated the feasibility of accurate sCT generation using a DL approach
Xue X et al. (China, 2021)	[59]	169	To develop DL approach to generate sCT images from nasopharyngeal treatments CBCT	Synthetic imaging generation Plan quality assurance and dose calculation	CBCT	The study demonstrated the feasibility of sCT generation using a DL approach with good dose calculation results (gamma pass rates ($> 95\%$)
Liu J et al. (China, 2021)	[60]	52	To develop DL approach to generate sCT images from nasopharyngeal treatments CBCT	Synthetic imaging generation	CBCT	The study demonstrated the feasibility of sCT generation
Zhang Y et al. (USA, 2021)	[61]	25	To develop DL approach to generate sCT images from H&N and pelvic treatments CBCT	Synthetic imaging generation	CBCT	The study demonstrated the feasibility of sCT generation
Chen L et al. (USA, 2020)	[62]	37	To develop DL approach to generate sCT images from CBCT	Synthetic imaging generation	CBCT	The study demonstrated the feasibility of sCT generation

Table 2 (continued)

First author (country/year)		No of patients	Objectives	Cluster area	IGRT modality	Conclusions
Uh J et al. (USA, 2021)	[63]	50	To develop DL approach to optimize CBCT quality for adaptive proton therapy in abdominal proton therapy in children and young adults	Synthetic imaging generation Plan quality assurance and dose calculation	CBCT	The study demonstrated the feasibility of CBCT optimization using a DL approach with good dose calculation results (gamma pass rates (98.5 ± 1.9%)
Lemus O M D et al. (USA, 2022)	[64]	17	To develop DL approach to generate sCT images from liver SBRT	Synthetic imaging generation Plan quality assurance and dose calculation	CBCT	The study demonstrated the feasibility of sCT generation using a DL approach with good dose calculation results (gamma pass rates (≥ 94.11%)
Wu W et al. (China, 2022)	[65]	153	To develop DL approach to generate sCT images from prostate CBCT	Synthetic imaging generation Plan quality assurance and dose calculation	CBCT	The study demonstrated the feasibility of sCT generation using a DL approach. Average structural similarity index measure between sCT and CBCT was higher than pCT
Kurosawa T et al. (Japan, 2020)	[66]	36	To improve the image quality of high-speed CBCT using a deep convolutional neural network in prostate cancer	Synthetic imaging generation	CBCT	The study developed a model to generate high-speed and high-quality CBCT
Thummerer A (the Netherlands, 2021)	[67]	27	To develop DL approach to generate sCT images from LUNG proton treatments	Synthetic imaging generation Plan quality assurance and dose calculation	CBCT	The study demonstrated the feasibility of sCT generation using a DL approach with good dose calculation results (gamma pass rates (96.8%)
Li Y et al. (China, 2019)	[68]	70	To develop DL approach to generate sCT images from nasopharyngeal treatments CBCT	Synthetic imaging generation	CBCT	The study demonstrated the feasibility of accurate sCT generation
Thummerer A (the Netherlands, 2020)	[69]	27	To develop DL approach to generate sCT images from H&N proton treatments	Synthetic imaging generation Plan quality assurance and dose calculation	CBCT	The study demonstrated the feasibility of sCT generation using a DL approach with good dose calculation results (gamma pass rates (96.1%)
Maspero M et al. (the Netherlands, 2020)	[70]	99	To investigate feasibility of applying a single convolutional network for dose calculation based on CBCT for H&N, lung, and breast cancer treatments	Plan quality assurance and dose calculation Synthetic imaging generation	CBCT	The study demonstrated the accuracy of generated sCT also for dose calculation
Sibolt P et al. (Denmark, 2021)	[71]	39	To demonstrate the feasibility of oART in pelvic district with autocontouring and autoplanning in CBCT-based AI solutions	Autosegmentation and Autoplanning	CBCT	The study demonstrated feasibility of oART in pelvic region. Adapted plan resulted to be superior in PTV coverage in 88% of cases
Li R et al. (USA, 2021)	[72]	16	To develop a DL method to predict tumor shrinking and generate CBCT-based autocontours	Autosegmentation and Autoplanning	CBCT	The study demonstrated a high prediction accuracy of target autocontours DL method (DSC 0.78–0.82

Table 2 (continued)

First author (country/year)		No of patients	Objectives	Cluster area	IGRT modality	Conclusions
Han X et al. (USA, 2021)	[73]	40	To develop a DL method for CBCT-based autocontours in pancreatic radiotherapy	Autosegmentation and Autoplanning	CBCT	The study demonstrated a high prediction accuracy of autocontours DL method for OARs (DSC 0.714 and 0.858 for bowel and stomach/duodenum)
Jiang J et al. (USA, 2021)	[74]	69	To develop a DL CBCT lung tumor segmentation method	Autosegmentation and Autoplanning	CBCT	The study demonstrated a high prediction accuracy of target autocontours
Alam S R et al. (USA, 2021)	[75]	191	To develop a method for esophagus autosegmentation in lung radiotherapy to prevent toxicity	Autosegmentation and Autoplanning Synthetic imaging generation	CBCT pCT	The study demonstrated a high accuracy of AS model for CBCTs-based RT (DSC 0.74–0.81)
Liang X et al. (USA, 2022)	[76]	251	To develop a DL method for CBCT-based contours propagation from pCT to CBCT in prostate radiotherapy	Autosegmentation and Autoplanning	CBCT	The study demonstrated a high prediction accuracy of DL contours propagation from pCT to CBCT method (DSC 0.85 ± 0.04)
Schreirer J et al. (Finland, 2020)	[77]	11	To develop a DL method for CBCT-based autocontours in prostate radiotherapy	Autosegmentation and Autoplanning	CBCT	The study demonstrated a high prediction accuracy of autocontours DL method for OARs (DSC 0.701 and 0.932)
Åström L M et al. (Denmark, 2022)	[78]	16	To evaluate the feasibility and dosimetric impact of CBCT-guided oART of urinary bladder cancer	Autosegmentation and Autoplanning	CBCT	The study demonstrated feasibility of oART in pelvic region. Adapted plan resulted to be superior in PTV coverage in 98% of cases
Wang C et al. (USA, 2020)	[79]	11	To develop a method for esophagus spatial changes evaluation in lung radiotherapy to prevent toxicity	Autosegmentation and Autoplanning Synthetic imaging generation	CBCT MRgRT	The study developed a model with high prediction of esophagus volume (>0.98)
Lalond A et al. (USA, 2020)	[80]	48	To develop a DL method to perform CBCT correction for adaptive proton radiotherapy in H&N	Plan quality assurance and dose calculation	CBCT	The study developed an accurate DL method for CBCT correction with dose calculation (gamma pass rates 98.89%)
Harms P et al. (USA, 2020)	[81]	23	To develop a DL method to perform online dose calculation from CBCT-based proton radiotherapy in H&N	Plan quality assurance and dose calculation	CBCT	The study developed an accurate DL method for CBCT-guided adaptive planning (MAE 0.06 ± 0.01, gamma passing rate 94%)
Luximon D C et al. (USA, 2022)	[82]	480	To develop a neural network to optimize and correct vertebral body misalignments in thoracic and abdominal radiotherapy	Delivery optimization	CBCT	The study developed a neural model with high accuracy (AUC > 99%) in identifying and correcting setup misalignments

Table 2 (continued)

First author (country/year)		No of patients	Objectives	Cluster area	IGRT modality	Conclusions
Liang X et al. (China, 2020)	[83]	6	To develop a DL model PTV localization on CBCT in prostate radiotherapy	Delivery optimization	CBCT	The study demonstrated the development of DL-based PTV localization technique showing strong correlations (> 0.94) in the couch shifts between model prediction and the reference
Fu Y et al. (USA, 2021)	[84]	50	To develop a DL method to register and deform MRI images to delineate clinical volumes on CBCT in prostate treatments	Delivery optimization	CBCT	The study demonstrated an accurate registration for CBCT contouring (DSC 0.93 ± 0.01)
Zhang S et al. (China, 2022)	[85]	45	To develop a CBCT radiomics-based model to determine ITV in lung radiotherapy	Delivery optimization	CBCT	The study showed a DL model to predict ITV variation in lung SBRT with good accuracy (DSC 0.83 ± 0.18)
Kai Y et al. (Japan, 2020)	[86]	20	To develop and test a ML model to predict target shifts in CBCT prostate radiotherapy	Delivery optimization	CBCT	The study demonstrated the accuracy of the model to predict the target shits (mean absolute residual errors were ≤ 1.04 mm)
Dohopolski M et al. (USA, 2022)	[87]	271	To develop a ML- and DL-based method to early identify cluster of H&N patients who will need feeding tube supplementation	Treatment response prediction	CBCT	The study developed a clinical and image-based model with good prediction accuracy (AUC 0.75)

Table 3 Articles regarding AI applied to MRgRT IGRT

First author (country/year)		No of patients	Objectives	Cluster area	IGRT modality	Conclusions
Cusumano D et al. (Italy,2020)	[5]	120	To develop a DL approach to generate sCT images from low field MR images in pelvis and abdomen	Synthetic imaging generation	MRgRT	The study demonstrated the feasibility of sCT generation using a DL approach for low field MR images in pelvis and abdomen, also showing a reliable calculation of IMRT plans in MRgRT
Scholey J E et al. (USA, 2022)	[52]	120	To implement an MR-only workflow by synthesizing MVCT from MRI	Synthetic imaging generation	CBCT and MRgRT	The study demonstrates the feasibility of using MRI-derived sMVCT in an MR-only treatment planning workflow
Sibolt P et al. (Denmark, 2021)	[71]	39	To demonstrate the feasibility of oART in pelvic district with autocontouring and autoplanning in CBCT-based AI solutions	Autosegmentation and Autoplanning	CBCT	The study demonstrated feasibility of oART in pelvic region. Adapted plan resulted to be superior in PTV coverage in 88% of cases
Wang C et al. (USA, 2020)	[79]	11	To develop a method for esophagus spatial changes evaluation in lung radiotherapy to prevent toxicity	Autosegmentation and Autoplanning Synthetic imaging generation	CBCT MRgRT	The study developed a model with high prediction of esophagus volume (> 0.98)
Lalond A et al. (USA, 2020)	[80]	48	To develop a DL method to perform CBCT correction for adaptive proton radiotherapy in H&N	Plan quality assurance and dose calculation	CBCT	The study developed an accurate DL method for CBCT correction with dose calculation (gamma pass rates 98.89%)
Harms P et al. (USA, 2020)	[81]	23	To develop a DL method to perform online dose calculation from CBCT-based proton radiotherapy in H&N	Plan quality assurance and dose calculation	CBCT	The study developed an accurate DL method for CBCT-guided adaptive planning (MAE 0.06 ± 0.01, gamma passing rate 94%)
Cusumano D et al. (Italy,2020)	[88]	26	To evaluate the dose calculation accuracy of using bulk sCT in presence of 0.35 T magnetic field in abdominal and pelvic adaptive RT	Synthetic imaging generation	MRgRT	The study demonstrates the reliability of generating synthetic CT using bulk RED assignment to address the inter-fraction variability in MR-guided radiotherapy
Lenkowicz J et al. (Italy, 2022)	[89]	60	To generate synthetic Computed Tomography (sCT) from 0.35 Tesla MRI of the thorax	Synthetic imaging generation	MRgRT	The study demonstrates the image and dose accuracy of generating synthetic CT for in lung MRgRT
Terpstra M A et al. (the Netherlands, 2020)	[90]	135	To develop and test a DL imaging reconstruction and motion estimation model for MRgRT	Synthetic imaging generation Delivery optimization	MRgRT	The study demonstrated the accuracy (root-mean-square error ± 1 mm) of DL-based image reconstruction and motion estimation for online adaptive MRgRT with minimal latency

Table 3 (continued)

First author (country/year)		No of patients	Objectives	Cluster area	IGRT modality	Conclusions
Chun J et al. (Korea, 2021)	[91]	50	To develop and test a DL high-resolution imaging reconstruction model for MRgRT	Synthetic imaging generation	MRgRT	The study demonstrated the generation of DL-based high-resolution imaging for online adaptive MRgRT with minimal latency
Olberg S et al. (USA, 2021)	[92]	33	To develop a DL approach to generate sCT images from low field MR images in abdomen	Synthetic imaging generation	MRgRT	The study demonstrated the feasibility of sCT generation using a DL approach for low field MR images in abdomen, with limitations for subset of patients with notable differences in intestinal gas
Olberg S et al. (USA, 2019)	[93]	1042 images	To develop a DL approach to generate sCT images from low field MR images in breast	Synthetic imaging generation	MRgRT	The study demonstrated the feasibility of sCT generation using a DL approach for low field MR images in breast and abdomen, also showing a reliable dose calculation ($\geq$98% passing rate for dose distribution)
Allan Thomas M et al. (USA, 2020)	[94]	53	To develop and test ML dose predicting model for adaptive MRgRT plan quality evaluation	Plan quality assurance and dose calculation	MRgRT	The study developed and tested a ML prediction model for 3D dose distribution in abdominal adaptive MRgRT (dose prediction error 0.1 ± 3.4 Gy)
Chen X et al. (China, 2022)	[95]	26	To develop autosegmentation (AS) framework for online delineation of prostate cancer using MRgRT	Autosegmentation and Autoplanning	MRgRT	The study developed an accurate segmentation model (DSC 0.79 to 0.93 for CTV) to shorten online adaptive MRgRT workflow
Tong N et al. (China, 2019)	[96]	25	To develop AS framework for H&N MRgRT	Autosegmentation and Autoplanning	MRgRT	The study tested a segmentation model for H&N delineation (DSC 0.6–0.916)
Friedrich F et al. (Germany, 2021)	[97]	50	To develop AS framework for online delineation in lung MRgRT	Autosegmentation and Autoplanning	MRgRT	The study developed a segmentation model for stomach delineation (DSC > 0.83)
Kawula M et al. (Germany, 2022)	[98]	92	To train convolutional neural networks (CNNs) for automatic segmentation of OARs and CTV for prostate cancer patients treated with 0.35 T MR-Linac	Autosegmentation and Autoplanning	MRgRT	The study demonstrated a high accuracy of AS model for OARs (DSC 0.88–0.93) and CTV (DSC 0.72–0.88)

Table 3 (continued)

First author (country/year)		No of patients	Objectives	Cluster area	IGRT modality	Conclusions
Chun J et al. (Korea, 2022)	[99]	60	To train AS framework in replanning CTs for traditional ART. To test AS in MRgRT and sCT generation	Autosegmentation and Autoplanning Synthetic imaging generation	pCT MRgRT	The study demonstrated a high accuracy of AS model for sCT-based RT (DSC 0.95). The developed model resulted in mean absolute error improvement for AS and sCT for MRgRT compared to conventional model
Liang F et al. (USA, 2018)	[100]	4	To develop autosegmentation (AS) framework for online delineation of abdominal district using MRgRT	Autosegmentation and Autoplanning	MRgRT	The study developed an accurate segmentation model (DSC above 0.86)
Eppenhof K A J et al. (the Netherlands, 2020)	[101]	5	To develop AS framework for online delineation of prostate cancer using MRgRT	Autosegmentation and Autoplanning	MRgRT	The study developed an accurate segmentation model (DSC 0.86 ± 0.05)
Künzel L A et al. (Germany, 2021)	[102]	1	To develop AS and autoplanning for prostate cancer MRgRT	Autosegmentation and Autoplanning	MRgRT	The study demonstrated the feasibility of an autonomous, un-supervised data preparation and plan generation for prostate MRgRT
Hague C et al. (UK, 2021)	[103]	30	To develop AS model for parotid and submandibular glands in H&N radiotherapy, comparing a CT-based to MR-based model	Autosegmentation and Autoplanning	MRgRT pCT	The study demonstrates better performance of the AS MR-based mode (DSC $\geq$ 0.80)
Chen Y et al. (USA, 2020)	[104]	102	To develop AS framework for online delineation of abdominal district in MRgRT	Autosegmentation and Autoplanning	MRgRT	The study developed an accurate segmentation model (DSC 0.80–0.96)
Huang L et al. (China 2021)	[105]	25	To develop AS framework for online delineation of stomach in MRgRT	Autosegmentation and Autoplanning	MRgRT	The study developed a segmentation model for stomach delineation (DSC 0.77)
Luximon D C et al. (USA, 2022)	[106]	116	To develop AS framework for online delineation of stomach in MRgRT	Autosegmentation and Autoplanning	MRgRT	The study developed a segmentation model for stomach delineation (Dice 0.91 ± 0.02)
Kajikawa T et al. (Japan, 2020)	[107]	50	To develop a DL-based dose distribution conversion approach for the correction of the influence of a magnetic field for online MRgRT in prostate cancer	Plan quality assurance and dose calculation	MRgRT	The study developed and tested a DL dose correction model for MRgRT (gamma indexes 94.95% $\pm$ 4.69%)
Li M et al. (Australia, 2020)	[108]	1	To develop a neural network to correct the geometric distortions in MR images in pelvic MRgRT	Plan quality assurance and dose calculation	MRgRT	The study demonstrated the feasibility of deep neural network for field deviations in the 1 T MRI-Linac system to optimize real-time MRgRT

Table 3 (continued)

First author (country/year)	No of patients	Objectives	Cluster area	IGRT modality	Conclusions
Cerviño L I et al. (USA, 2011) [109]	5	To develop and test a template matching (TM) and an artificial neural network (ANN) tumor-tracking system in lung MRgRT	Delivery optimization	MRgRT	The study demonstrated a high accuracy in template matching (TM) algorithm in combination with surrogate tracking using the diaphragm
Liu L et al. (USA, 2022) [110]	7	To develop a DL tumor-tracking system in MRgRT	Delivery optimization	MRgRT	The study demonstrated an accuracy in DL GTV tracking with 0.4 ± 0.3 mm and 0.5 ± 0.4 mm median distance for cine and radial acquisitions
Gao Y et al. (USA, 2021) [111]	30	To predict soft tissue sarcoma response using a novel deep-learning prediction framework in MRgRT	Treatment response prediction	MRgRT	The study demonstrated the accuracy of DL in predicting pathologic response from longitudinal DWI (97.1% and patient-based prediction)

AI Artificial Intelligence, *AS* Auto Segmentation, *AUC* area under the curve, *CBCT* Cone Beam Computed Tomography, *CCR* Clinical Complete Response, *CRT* Chemo-Radiotherapy, *DFS* Disease Free Survival, *DL* Deep Learning, *H&N* Head and Neck, *ITV* Internal Target Volume, *LC* Local Control, *LF* Local Failure, *MVCT* Mega Voltage Computed Tomography, *MRgRT* Magnetic Resonance-guided Radiation Therapy, *MRI* Magnetic Resonance Imaging, *oART* online Adaptive Radiation Therapy, *OS* Overall Survival, *PC* Prostate Cancer, *pCT* planning Computed Tomography, *PDAC* Pancreatic Ductal AdenoCarcinoma, *PFS* Progression Free Survival, *PTV* Planning Target Volume, *SBRT* Stereotactic Body Radiation Therapy, *sCT* synthetic Computed Tomography

Conventional radiomics is based on the extraction of quantitative image features from a region of interest (ROI) with the subsequent creation of a model correlated with clinical endpoints. In this context, delta-radiomics analyzes the temporal variation of radiomic features to assess sensitivity during treatment of the tumor understood as a heterogeneous entity [8].

Specific biomarkers of treatment response can be identified in this context. One of these is the early regression index (ERITCP) whose validity has been demonstrated, for example, in locally advanced rectal cancer. This index models the radiobiologic behavior of the tumor by considering its volumetric regression from simulated treatment (Vpre) to mid-treatment (Vmid) [112]. Promising results have been shown in the analysis of features in MRI-guided treatments of rectal and pancreatic cancer, evidence have shown that delta-radiomics could predict cCR and pCR (AUC 0.81) in rectal cancer and LC (AUC 0.79) in pancreatic cancer [9, 11].

Several settings have been investigated by the authors, varying from the possibility to correlate treatment data to clinical outcomes or exploiting innovative optimization approaches.

In the largest number of analyzed studies, radiomics and AI aim to lead to optimized stratification of patients with the goal of better defining their risk category and tailoring treatment models accordingly. The input information derived from IGRT image analysis also allows to develop response prediction models for response to treatments.

The availability of such models can radically modify the foreseen therapeutic strategies, proposing online plan re-optimization or dose modifications.

Several experiences also correlated data extracted from in-room IGRT-derived images to the onset of treatment-related toxicities in different sites, suggesting the need for improvement strategies in terms of dose delivery accuracy, made possible by the most modern delivery technologies.

Cone Beam CT-based radiomics analysis showed good results in terms of treatment outcomes prediction, with a major interest in toxicity prediction in head and neck and thoracic malignancies [37, 40, 41]. Interestingly, some very recent studies have proposed the application of radiomics-based predictive models on in-room MRI images, showing an overall high level of prediction of tumor response in different sites also in this innovative treatment IGRT framework [11, 32, 33].

The development of AI-based systems and radiomics that can predict treatment outcomes may further support the development of innovative adaptive radiotherapy approaches, suggesting the need for dose adaptation to poor-responder patients [113]. This approach represents the backbone of a first prospective interventional clinical trial that uses image derived biomarkers to stratify patients undergoing neoadjuvant chemoradiotherapy for locally advanced rectal cancer on a 0.35 T MR Linac in risk classes and guiding dose escalation protocols, introducing a brand new concept of clinical trials in RT [114].

The applications of AI techniques also play an emerging role in optimizing the different phases of radiation treatment by increasing safety and standardization. One of the most optimizable areas is reducing the time required for workflow. This aspect is even more crucial in MRI-guided treatments, which have been shown to be time-consuming processes in different experiences [115–117]. Autosegmentation and autoplanning models speed up the planning steps while providing a high standard of quality and consistent performances, less prone to interobserver variability.

Reducing treatment times through AI applications, particularly in online adaptive treatments, also has the advantage of increasing patient's compliance to treatment, offering more tolerable treatment sessions.

Besides the clinical advantages, applying AI-based quality assurance (QA) tools to the different phases of radiation treatment planning and delivery is another central area of investigation and research. In this context, there are growing experiences in developing methods for creating synthetic imaging from in-room IGRT images to optimize dose calculation on the patient's daily anatomy and disclose unprecedented approaches for online adaptation.

In conclusion, the evidence available in the literature is based on small retrospective datasets but describes a significant impact of radiomics and AI applied to modern in-room IGRT methods in all the phases of radiation treatment.

Further confirmation about the potentialities of these tools will come from prospective studies of correlation with clinical outcomes and gold standard treatment workflows and strategies.

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