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Review Article

A decade of radiotherapy: Clinical evolution, technological innovation, and the challenge of cardiotoxicity

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ABSTRACT

Radiotherapy transformed in 2015–2025, moving from incremental change to biologically informed, image-guided and increasingly automated care. This narrative review, informed by a comprehensive literature search of major databases (2015–2025), synthesises advances across clinical practice, technology, and translational science, with particular attention to radiation-induced cardiotoxicity as a key survivorship challenge. Randomised evidence established hypofractionation and stereotactic body radiotherapy as standards in selected breast, prostate and oligometastatic settings, improving efficiency without compromising control. Technological frontiers include MR-guided online adaptive radiotherapy for real-time plan modification, global expansion of proton therapy for paediatric indications and some adults, emerging biologically-guided radiotherapy (BgRT) platforms, expanding applications of radiopharmaceutical therapy (RPT), and early human feasibility of ultra-high dose-rate FLASH that may widen the therapeutic window. Artificial intelligence streamlines auto-segmentation, planning and quality assurance, while radiogenomics, radiomics and immuno-radiotherapy combinations advance personalization. Amid these gains, late cardiovascular effects demand urgent focus: radiation-induced cardiotoxicity spans coronary, myocardial, valvular and conduction injury, with risk linked to dose-volume exposure and systemic co-therapies. Mitigation integrates deep-inspiration breath-hold, motion management, cardiac substructure contouring, proton techniques and biomarker-informed risk stratification. Persistent global access disparities, workforce shortages, and cost-effectiveness challenges highlight the need for pragmatic adoption of efficient regimens, equitable infrastructure investment, and supportive policy frameworks including AI-enabled remote planning and cloud-based quality assurance. This review synthesises advances, appraises cardiotoxicity evidence and countermeasures, and prioritises: integrate multi-omic biomarkers with adaptive, AI-enabled delivery; translate FLASH rigorously; build long-term cardio-oncology data; and implement policies extending modern radiotherapy beyond high-income settings. Radiotherapy is set to become more precise, personalized and equitable.

1. Introduction

Radiotherapy remains a fundamental pillar of modern cancer care, with approximately half of all patients requiring radiation at some point in their treatment journey [1,2]. Over the last century, the field has advanced through landmark innovations, from the discovery of X-rays to the introduction of linear accelerators, CT-based planning, and more recently, intensity-modulated (IMRT) and image-guided radiotherapy

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(IGRT). Each of these milestones has progressively enhanced precision and safety, consolidating radiotherapy as a cornerstone of curative and palliative oncology.

The last decade (2015–2025) represents a particularly dynamic era, marked by rapid and parallel progress across three domains: robust clinical evidence reshaping disease-specific practice, technological leaps that have redefined delivery, and deepening biological insights that are shifting treatment toward personalization. Hypofractionation exemplifies this shift; randomized trials such as FAST-Forward demonstrated that ultra-hypofractionated schedules are non-inferior to conventional regimens in breast cancer, transforming standard practice and improving treatment efficiency [3]. Likewise, stereotactic ablative radiotherapy (SABR) has emerged as a paradigm-changing approach for oligometastatic disease, with the SABR-COMET trial reporting durable overall survival gains [4].

Technological innovation has matched these clinical advances. The advent of magnetic resonance–guided linear accelerators (MR-linacs) has enabled daily adaptive planning with unparalleled anatomical visualization [5], while global expansion of proton therapy has extended precision options for paediatric and select adult populations [6]. Emerging biologically-guided radiotherapy platforms that leverage real-time PET signals represent the next frontier in tumour-tracking precision. Meanwhile, the early feasibility of ultra-high dose-rate "FLASH" radiotherapy suggests the possibility of a paradigm shift in normal tissue protection [7]. Simultaneously, artificial intelligence (AI) is reshaping workflows through auto-contouring, treatment optimization, and quality assurance, although concerns around validation, generalizability, and governance remain [8].

Yet, with extended survivorship, late toxicities are assuming increasing importance in the discourse on radiotherapy's future. Among these, radiotherapy-induced cardiotoxicity has emerged as a central concern, particularly in breast, thoracic, and lymphoma patients where proximity of the heart to target volumes presents unavoidable risks. Radiation exposure to the heart and coronary arteries is associated with increased risks of ischemic heart disease, arrhythmias, and heart failure, even at relatively low mean doses [9]. The recognition of these risks has catalysed the integration of cardiac-sparing techniques such as deep inspiration breath hold, advanced motion management, and proton therapy. More recently, AI-driven segmentation of cardiac substructures and predictive modelling of dose-toxicity relationships have further enhanced efforts to mitigate these risks [10]. Thus, the evolution of radiotherapy is no longer defined solely by gains in tumour control but equally by its ability to minimize harm to critical organs and safeguard long-term quality of life.

Despite these transformative strides, profound inequities in global access to radiotherapy persist. Many low- and middle-income countries face chronic shortages of equipment, personnel, and training, leaving patients unable to benefit from modern technologies or cardioprotective strategies. The Lancet Oncology Commission [11] has emphasized that investment in radiotherapy infrastructure remains among the most cost-effective means of reducing global cancer mortality, underscoring the ethical imperative to extend advances beyond high-income settings.

This narrative review synthesises the clinical, technological, and biological innovations that have defined radiotherapy between 2015 and 2025, while explicitly addressing the emerging challenge of radiation-induced cardiotoxicity as a key survivorship outcome. We organize the discussion across five domains: (i) clinical evolution, (ii) technological frontiers, (iii) biological and translational insights, (iv) radiation-induced cardiotoxicity and mitigation strategies, and (v) emerging frontiers including the role of AI in radiotherapy and future directions. By mapping progress in these areas, the review aims to inform practitioners, researchers, and policymakers of how radiotherapy is evolving into a discipline that is more precise, biologically informed, and computationally integrated, yet also accountable for survivorship outcomes and equitable access.

2. Methods

2.1. Search strategy and data sources

A comprehensive literature search was performed across major electronic databases including PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Library to identify relevant publications between January 2015 and July 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords related to radiotherapy, technological advances, biological insights, and treatment-related toxicities. Key terms included: "radiotherapy", "hypofractionation", "stereotactic body radiotherapy", "proton therapy", "FLASH radiotherapy", "magnetic resonance guided radiotherapy", "artificial intelligence", "machine learning", "radiogenomics", "radiomics", "radiopharmaceutical therapy", "theranostics", "biologically guided radiotherapy", and "radiation-induced cardiotoxicity".

To complement database searches, conference proceedings from major oncology and radiation oncology societies (ASTRO, ESTRO, ASCO, ESMO) were reviewed, along with regulatory agency reports (FDA, EMA) and international clinical trial registries (ClinicalTrials.gov, EudraCT). Reference lists of relevant systematic reviews and meta-analyses were hand-searched to ensure comprehensive coverage of emerging evidence.

2.2. Study selection and inclusion criteria

Eligible studies included peer-reviewed original research articles, randomized controlled trials, large prospective and retrospective cohort studies, systematic reviews, meta-analyses, and authoritative consensus guidelines published in English. We prioritized high-impact evidence addressing:

- Clinical advances in radiotherapy fractionation and disease-specific practice.
- Technological innovations such as adaptive radiotherapy, particle therapy, biologically-guided platforms, and FLASH irradiation.
- Translational and biological insights including radiogenomics, radiomics, radiopharmaceutical therapy, and immunotherapy combinations.
- Evidence on radiotherapy-induced cardiotoxicity, encompassing risk mechanisms, dose–response relationships, clinical outcomes, and mitigation strategies.
- Applications of artificial intelligence and machine learning in treatment planning, toxicity prediction, and workflow optimization.

Exclusion criteria were preclinical studies without translational relevance, small case reports (<20 patients), duplicate publications, and studies focusing exclusively on radiotherapy physics without clinical or biological context.

2.3. Data extraction and narrative synthesis

This review employed a narrative synthesis approach rather than systematic review methodology. Data were extracted qualitatively using a standardized framework that captured study design, patient population, cancer type, intervention details, treatment modality, outcomes assessed (tumour control, survival, toxicity, cardiotoxicity), and methodological characteristics. Special emphasis was placed on:

- Randomized controlled trials informing practice-changing hypofractionation or SABR strategies.
- Prospective registries and real-world data evaluating MR-linac and proton therapy outcomes.
- Translational studies on biomarkers, radiogenomics, and radiomics predictive of treatment response and toxicity.

- Studies quantifying cardiac dose–volume metrics and their association with cardiotoxicity.
- Applications of AI in cardiac-sparing techniques, contouring accuracy, and predictive modelling.

Given the narrative approach, formal quality appraisal tools (Cochrane risk-of-bias, Newcastle-Ottawa Scale, QUADAS-2) were not systematically applied to all included studies. However, we prioritized high-quality randomized controlled trials, large prospective cohorts, and authoritative consensus guidelines where available, and contextualized findings from observational studies and early-phase trials accordingly.

2.4. Data synthesis and analysis

Given the heterogeneity of study designs, tumour types, and endpoints, a narrative synthesis was employed as the primary analytical approach. Evidence was organized into thematic domains. Within each domain, findings were integrated to highlight key advances, limitations, and ongoing controversies.

Emphasis was placed on radiotherapy-induced cardiotoxicity, where data from clinical cohorts, dose-volume studies, and AI-driven predictive models were synthesized to provide an updated understanding of incidence, mechanisms, and mitigation. Evidence from studies demonstrating advances in modern cardioprotective radiotherapy techniques were synthesized to draw translational insights.

This review adopted certain PRISMA principles for transparency in literature identification but did not conduct a formal systematic review with meta-analysis, given the aim to provide a broad, integrative narrative across multiple domains of radiotherapy evolution. No PRISMA flow diagram or formal risk-of-bias assessment is presented, consistent with the narrative review design.

3. Clinical evolution (2015–2025)

3.1. Hypofractionation and the changing fractionation paradigm

One of the most significant shifts in radiotherapy practice over the past decade has been the adoption of hypofractionated schedules as standard of care in several common malignancies. Historically, conventional fractionation of 1.8–2 Gy per day was guided by radiobiological principles and normal tissue tolerance [12]. However, large, randomized trials have now demonstrated that shorter schedules can achieve equivalent outcomes with improved patient convenience and resource efficiency [13].

In early-stage breast cancer, the UK FAST-Forward trial compared 26 Gy in five fractions over one week against the conventional 40 Gy in 15 fractions. At five years, the trial reported non-inferior local tumour control and comparable late toxicity [3]. These findings, combined with earlier Canadian and UK hypofractionation studies, have established one-week schedules as a new international standard. Importantly, adoption was accelerated during the COVID-19 pandemic, when reducing hospital visits became a priority for patient safety [3].

Prostate cancer has similarly undergone a fractionation transformation. The HYPO-RT-PC trial in intermediate to high-risk disease demonstrated that ultra-hypofractionation (42.7 Gy in seven fractions) was non-inferior to conventional schedules in terms of failure-free survival and toxicity [14]. Subsequent data from the PACE-B trial confirmed the safety of stereotactic body radiotherapy (SBRT) for localized prostate cancer, reporting low rates of acute genitourinary and gastrointestinal toxicity [15]. Together, these results have redefined prostate radiotherapy by supporting SBRT as a standard treatment option in appropriately selected patients.

In locally advanced lung cancer, the landmark PACIFIC trial established concurrent chemoradiotherapy followed by durvalumab immunotherapy as a new standard of care, demonstrating significant progression-free and overall survival benefits [16]. Efforts to improve local control with radiation dose escalation have been cautionary: RTOG 0617 found 74 Gy (vs 60 Gy) with concurrent chemotherapy resulted in worse overall survival, highlighting the toxicity–efficacy tradeoff [17]. Adaptive/PET-guided radiotherapy has shown multicenter feasibility, but randomized testing has not shown clear outcome gains to date (NRG-RTOG 1106/EA 6697) [18].

For head and neck cancers, the past decade has seen refinement of IMRT techniques to reduce xerostomia and dysphagia, alongside emerging evidence for de-intensification strategies in HPV-positive oropharyngeal cancer. Trials such as NRG-HN002 are investigating whether reduced-dose radiotherapy can maintain efficacy while limiting long-term toxicity in this favorable-risk population [19]. Re-irradiation for recurrent head and neck cancer has also advanced, with SBRT and proton therapy enabling safe retreatment in previously irradiated fields. SBRT-based salvage regimens show prospective feasibility in selected patients [20], and proton therapy cohorts suggest potential for better normal-tissue sparing during retreatment with meaningful control but ongoing risk of serious toxicity [21].

3.2. Expansion of stereotactic body radiotherapy (SBRT)

SBRT, initially developed for medically inoperable early-stage lung cancer, has expanded across multiple disease sites, including liver, pancreas, kidney, and spine. The most transformative application, however, has been in the management of oligometastatic disease.

The landmark SABR-COMET trial randomized patients with one to five metastatic lesions to receive either standard of care or stereotactic radiotherapy to all sites of disease. At five years, SABR was associated with a 25% absolute improvement in overall survival [4]. While sample size was modest, the trial provided compelling evidence that local ablative therapy could meaningfully alter the natural history of metastatic cancer. Subsequent studies such as NRG-BR002 are refining the role of SBRT in specific settings, particularly breast and prostate oligometastases.

These findings have catalysed a shift in oncology thinking from palliative management of metastatic disease to selective curative intent in the oligometastatic state. The biological underpinnings of this paradigm suggesting a distinct metastatic biology with limited systemic potential remain under investigation, but clinical adoption is already accelerating.

3.3. Integration with systemic therapy

Radiotherapy has increasingly been combined with novel systemic agents, most notably immunotherapies. Preclinical studies and early clinical reports have described the so-called “abscopal effect,” whereby local radiotherapy induces systemic immune activation [22]. Although robust clinical evidence remains limited, multiple ongoing trials are evaluating the combination of radiotherapy with immune checkpoint inhibitors across tumour types, including lung, head and neck, and melanoma.

In parallel, the combination of radiotherapy with DNA damage repair inhibitors, such as PARP inhibitors and ATR inhibitors, is under active study. These approaches are motivated by mechanistic synergy between DNA damage induced by radiotherapy and impaired repair pathways targeted by systemic therapy [23]. Early-phase trials have demonstrated feasibility, though late toxicity risks require careful evaluation.

4. Technological advances

4.1. Image-guided and adaptive radiotherapy

Image-guided radiotherapy (IGRT) has become a cornerstone of modern radiotherapy. Historically, treatment relied on bony landmarks

or simple portal imaging, leading to significant uncertainties in target positioning. The integration of cone-beam CT (CBCT), volumetric imaging, and increasingly MRI into the treatment workflow has dramatically improved tumour localization and reduced planning margins, allowing dose escalation while minimizing toxicity [24].

Adaptive radiotherapy (ART) represents the next step, adjusting treatment plans dynamically to account for anatomical changes during therapy. Daily variations in tumour volume, organ motion, or patient positioning can now be compensated for with on-table plan adaptation. ART can be implemented offline, with between-fraction replanning to address systematic/progressive changes over the treatment course (e.g., tumour shrinkage and weight loss), or online, with on-table "anatomy-of-the-day" replanning immediately before a fraction using in-room imaging, most commonly MR-guided systems and increasingly CBCT-guided platforms [25].

4.2. MR-linac: clinical translation

The integration of high-resolution MRI with linear accelerators has enabled true online adaptive radiotherapy. MR-linacs offer soft-tissue contrast superior to CT, allow real-time tumour tracking, and facilitate plan adaptation on the day of treatment. Early results from the 'MOMENTUM registry', a multi-centre international initiative, report that online adaptive workflows are feasible, safe, and deliver improved target coverage in anatomically challenging tumours such as pancreatic and liver cancers [26,27]. Dosimetric work on MR-Linac/online adaptive MR-guided RT consistently shows better sparing of nearby organs at risk while maintaining target coverage. Particularly in pancreatic SBRT, daily adaptation can lower duodenum, stomach, and small-bowel doses resulting in lower rates of severe (grade $\geq$3) GI toxicity when constraints are met [28]. In liver RT, MR-Linac real-time imaging and respiratory gating can reduce motion margins and thereby decrease irradiation of uninvolved (healthy) liver parenchyma, supporting safer dose delivery in a moving target [29]. Table 1 summarizes key MR-Linac platforms, detailing their magnetic field strengths, types of adaptation used, target disease sites, and notable features for each system.

MR-Linac advantages include high-contrast real-time MR guidance that can reduce margins and normal-tissue irradiation, enabling tighter OAR sparing and potential dose escalation, and it can support functional/quantitative MRI integration (e.g., diffusion/perfusion) within adaptive workflows [31]. However, key limitations are longer on-table times (often ~30–60 min per fraction for MRI-guided workflows, and longer for online adaptation) and resource-intensive multidisciplinary staffing (including physician, therapists, physicist/dosimetry support for adaptive sessions) [31]. Capital costs are also higher: MR-Linac acquisition is commonly cited as >$7.5M (e.g., $7.8M for an MRIdian in one costing study), versus conventional linacs in the low-single-digit millions (e.g., £1.73M NHS procurement estimate; $4.75M for a high-end conventional configuration in one study) [31,35,36]. Economic "offsets" are plausible. For example, fewer fractions/hypofractionation can increase capacity, but formal cost-effectiveness evidence is still limited and highly assumption-dependent which is often hinging on toxicity/complication reductions.

Table 1
Key MR-Linac platforms and features.

Platform	Magnetic Field	Adaptation Type	Target Disease Sites	Notable Features
Elekta Unity [30,31]	1.5 T	Online	Pancreas, liver, prostate, lung	Integrated MRI, auto-contouring, ATP/ATS workflow
ViewRay MRIdian [31,32]	0.35 T	Online	Pancreas, liver, lung, oligometastases	Cine-MRI gating, adaptive planning
Hybrid research platforms [33,34]	Variable	Online/ offline	Research settings	Early prototypes for research

ATP = Adapt to Position; ATS = Adapt to Shape.

4.3. Proton therapy

Proton therapy leverages the Bragg peak phenomenon to deposit maximum energy at a defined depth, sparing distal normal tissues. Pediatric oncology remains the clearest beneficiary, with significant reductions in late toxicity and secondary malignancy risk [37]. For adults, evidence is strongest for head and neck tumours, especially nasopharyngeal, paranasal sinus, and skull base tumours [38], as well as re-irradiation scenarios where proton therapy can safely deliver high doses in anatomical regions where photon therapy would be limited by prior exposure [39].

Table 2 presents selected proton therapy clinical trials and studies across various tumour types, summarizing sample sizes and key outcomes related to treatment efficacy, toxicity, and comparative benefits versus photon-based therapies.

Key limitations of proton therapy include high capital and operating costs, limited geographic access, and the need for specialized shielding/infrastructure and staffing. Historically, multi-room proton centers have often been cited in the ~$150–200M range to build [46], although newer single-room concepts can be as low as $40 to $50 million [47]. Treatment delivery is typically more expensive than advanced photon RT in many settings. For example, one cost-effectiveness analysis used ~$31,400 for proton therapy vs ~$16,000 for IMRT (oesophageal cancer model) [48]. Although, this can vary from region to region. While dosimetric advantages (normal-tissue sparing) are well established for supporting strong rationale in paediatrics and re-irradiation, the cost-effectiveness in many adult cancers remains debated and is sensitive to assumptions about toxicity reduction and long-term outcomes. Consequently, comparative effectiveness trials are ongoing to define adult indications where protons provide clear clinical benefit over IMRT/photon techniques, e.g., NRG-GI006 (protons vs IMRT for oesophageal cancer) and other randomized comparisons emerging in breast and additional disease sites [49].

4.4. FLASH radiotherapy

FLASH radiotherapy delivers radiation at ultra-high dose rates (>40 Gy/s), demonstrating the ability to spare normal tissue while maintaining tumour control in preclinical models [50]. This means that the same fraction can be delivered in milliseconds rather than minutes. Conceptually, if the "FLASH effect" translates to humans as preferential normal-tissue sparing at the same tumor dose, the normal-tissue dose--volume histogram (DVH) would shift leftward (i.e., a smaller volume of normal tissue receives moderate-to-high dose) compared with conventional delivery. This is illustrated in Fig. 1. Initial human feasibility experience suggests FLASH is technically deliverable and generally well tolerated, including electron FLASH for cutaneous lymphoma and proton FLASH for painful extremity bone metastases [51,52].

Proposed mechanistic effect include transient radiolytic oxygen depletion, altered free-radical/ROS chemistry (e.g., radical-radical recombination and changes in oxidative species production), and immune-related sparing with multiple modelling and preclinical studies suggesting reduced irradiation of circulating immune cells/lymphocytes compared with conventional dose rates [53]. However, the FLASH effect is not yet mechanistically settled, and rigorous validation in humans remains needed.

Challenges to broader clinical implementation include standardizing dose-rate measurements and beam quality, ensuring reproducibility across photon, electron, and proton platforms, elucidating the biological mechanisms underlying the FLASH effect (oxygen depletion, radical chemistry, and immune modulation are proposed), and addressing the

Table 2
Select proton therapy trials and outcomes.

Tumour Type	Study/Trial	N (approx.)	Key Outcome	Evidence Level
Prostate [40]	PARTIQoL, Phase III randomized trial comparing proton beam therapy (PBT) vs IMRT.	450	No clinically meaningful difference in patient-reported quality of life or short-term toxicity between PBT and IMRT; both arms show excellent tumour control at reported follow-up.	Level I: Randomized, comparable outcomes
Pediatric CNS [41]	Pediatric Proton Consortium Registry (PPCR), multi-institutional prospective registry	1000+	Registry data indicate reduced radiation-related late effects (neurocognitive, endocrine, hearing) with PBT compared with historical photon cohorts; supports preferential use of protons in many pediatric CNS tumours.	Level II-III: Registry data, clear benefit established
Head & Neck (paranasal/ sinonasal) [38]	Systematic review & meta-analysis of charged particle (proton/carbon) vs photon therapy	pooled (various series)	Non-randomized data and pooled analyses suggest improved local control and/or reduced severe toxicity for charged-particle therapy in anatomically complex sinonasal tumours, but evidence derives mainly from observational series.	Level III: Observational, suggestive benefit
Oesophageal [42]	Randomized Phase IIb trial: PBT vs IMRT for locally advanced oesophageal cancer.	145–220 (trial randomized subset)	Proton therapy reduced treatment-related adverse events (grade ≥3) and some perioperative complications compared with IMRT while preserving similar progression-free and overall survival.	Level II: Randomized Phase IIb, toxicity benefit demonstrated
Oesophageal (meta-analysis) [43]	Systematic review & meta-analysis	pooled studies (45 studies)	Meta-analysis reported reduced OAR doses and lower rates of some toxicities with proton therapy vs photon therapy and suggested potential survival benefit in pooled data. Although study heterogeneity may limit generalisation of findings.	Level III: Pooled data, heterogeneity limits interpretation
Breast [44,45]	Ongoing Pragmatic randomized clinical trial: Proton Vs Photon for Patients with non-metastatic breast cancer and systematic reviews	various small cohorts; no completed phase III RCTs showing superiority	There are no completed large, randomized trials conclusively demonstrating superiority of PBT over modern photon techniques in early-stage breast cancer; ongoing studies and systematic reviews report comparable toxicity and local control to photons in reported cohorts.	Level III-IV: Ongoing trials, no clear superiority yet established

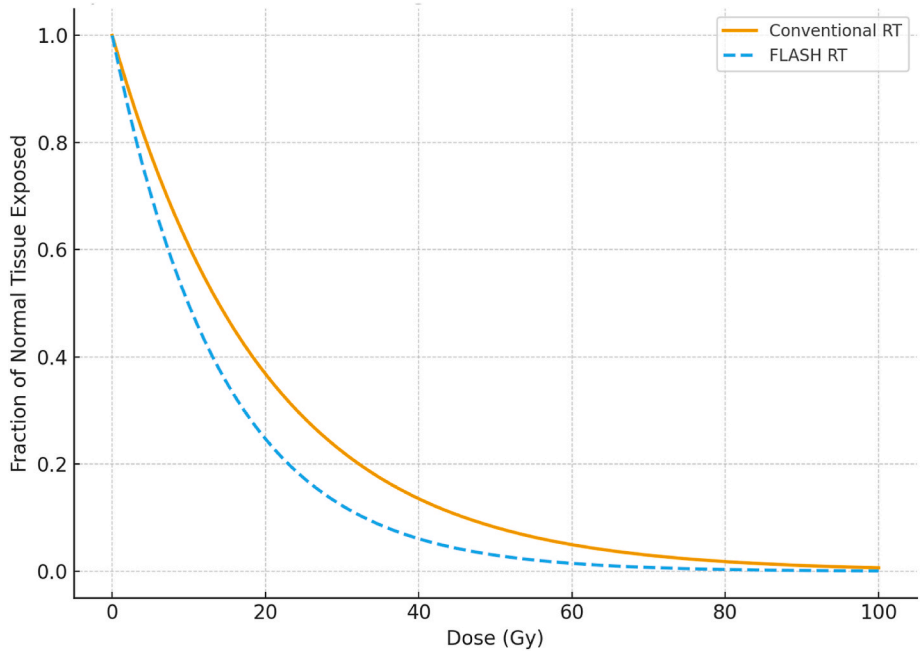

Fig. 1. Conceptual DVH comparing normal tissue dose between conventional and FLASH radiotherapy. Conceptually, if FLASH produces a normal-tissue sparing effect, the normal-tissue DVH shifts left (less normal tissue receives moderate-to-high dose) compared with conventional RT for the same intended tumor dose.

substantial technical challenge of delivering FLASH to deep-seated tumours with adequate dose conformity, which requires sophisticated beam-shaping technologies and rigorous dosimetric verification.

4.5. Artificial intelligence and automation

Artificial intelligence has become a transformative tool in radiotherapy planning, contouring, and QA. Key applications include auto-segmentation, where deep learning models reduce contouring time and inter-observer variability [54]; automated planning, where machine learning predicts achievable dose distributions and assists in optimization [55]; and outcome and toxicity prediction, which integrates radiomics and clinical data to personalize treatment [56].

AI adoption is growing, but challenges remain especially in ensuring generalizability across institutions, maintaining transparency in decision-making, and establishing governance frameworks to regulate clinical use. AI used in healthcare is increasingly expected to operate under meaningful human oversight rather than as an autonomous

decision-maker. In the EU, the AI Act explicitly requires "human oversight" for high-risk AI systems (often framed operationally as *human-in-the-loop* controls such as review, the ability to intervene, and using outputs appropriately) [57]. Questions of legal liability for AI-generated errors and the need for algorithmic transparency remain areas of active policy development, with regulatory bodies increasingly requiring prospective validation datasets and ongoing performance monitoring for deployed systems. Table 3 outlines key AI applications in the radiotherapy workflow, highlighting example tools and their clinical impacts such as time savings, plan optimization, and early toxicity prediction.

4.6. Biologically guided radiotherapy (BgRT)

BgRT is an emerging step beyond purely anatomical image guidance, aiming to steer radiation using tumour biology signals rather than geometry alone. The best-developed example is the RefleXion X1 "PET-linac" concept, which integrates PET detection with a linac so that annihilation photons from PET-avid disease can be used as a biological beacon to guide beamlet delivery with sub-second latency, enabling motion-robust targeting in principle without relying only on CT/MR surrogates [59,60]. Unlike MR-linacs, which primarily improve visualization of soft tissue anatomy, BgRT is explicitly designed to leverage metabolic/biologic activity (most commonly FDG, with active exploration of other tracers such as PSMA) to support real-time tracking and potentially differential dosing of biologically heterogeneous disease [60,61].

Early planning/technical feasibility studies suggest BgRT could be useful where anatomic boundaries are uncertain or where functionally active burden extends beyond structural imaging; but issues often raised include oligometastatic disease and mobile thoracic targets, where PET emissions could help manage motion during delivery [60,62]. However, the evidence base is still early-stage, and several practical constraints are repeatedly highlighted: BgRT performance depends on PET signal strength and contrast, making signal-to-noise and low-uptake/small-target feasibility nontrivial (e.g., relationships between SUV/target size and deliverability) [63]. In addition, the field still needs consensus and validation around biological target volume definitions and robust quality assurance/commissioning frameworks tailored to real-time PET-driven delivery. As with other major platform shifts in image guidance, rigorous prospective clinical trials and standardized monitoring will be essential to define where BgRT provides clear benefit over established anatomic or hybrid (PET-informed planning) approaches.

Table 3
AI applications in radiotherapy workflow.

Application	Example Tool/ Vendor	FDA/EMA Approval Status	Clinical Impact
Auto-contouring [58]	Varian Ethos, MVision, Limbus AI (FDA 510(k)), MIM Contour ProtégéAI (CE Mark)	FDA 510(k)/ CE Mark approved	Reduces contouring time by 50–70%, improved inter-observer consistency
Plan optimization [55]	RaySearch, Pinnacle Auto-Planning, RapidPlan (Varian)	FDA cleared/ CE Mark	Improves plan consistency, reduces planning time, dosimetric quality comparable or superior to manual planning
Toxicity/ outcome prediction [56]	In-house ML models, emerging commercial platforms under validation	Research/ validation stage	Early prediction of esophagitis, xerostomia, cardiac events; enables personalized dose constraints

4.7. Radiopharmaceutical therapy (RPT) and theranostics

Although this review focuses on external beam radiotherapy (EBRT), the past decade has seen rapid growth in RPT and theranostics, which pair diagnostic imaging and targeted radionuclide treatment to personalize systemic radiation delivery. Particularly, this treatment modality is valuable when disease burden is diffuse or extends beyond what EBRT can reasonably encompass. Clinically, the strongest modern example is ˆ177Lu-PSMA-617 for PSMA-positive metastatic castration-resistant prostate cancer (mCRPC): the phase III VISION trial showed that adding ˆ177Lu-PSMA-617 to standard of care significantly improved radiographic progression-free survival and overall survival, establishing radioligand therapy as a consequential systemic option in advanced prostate cancer [64]. Another pivotal agent is ˆ223Ra (radium-223) dichloride, an alpha-emitter approved for symptomatic, bone-predominant mCRPC without known visceral metastases; in ALSYMPCA, radium-223 improved overall survival versus placebo while also delaying skeletal events [65].

Integration of RPT with EBRT is now an active combined-modality frontier in oncology. For example, using EBRT/SBRT to ablate symptomatic or oligoprogressive sites while RPT provides systemic control, but the evidence base is still developing and tends to be dominated by feasibility/retrospective experience and emerging safety reports rather than definitive randomized data [66]. A key technical challenge is cumulative dosimetry: combining internal (systemic) and external radiation requires careful accounting of absorbed doses to shared organs-at-risk (e.g., marrow, kidneys, salivary glands, bowel) and thoughtful sequencing, an area where methodology exists but remains inconsistently implemented across trials and practice [67]. Overall, theranostics represent a genuine shift toward biologically personalized, whole-body radiation medicine, but defining where combinations with EBRT improve outcomes (beyond palliation/local control) will depend on rigorous prospective studies and standardized dosimetry with toxicity monitoring.

5. Biological and translational insights

5.1. Radiogenomics: toward personalized radiotherapy

Radiogenomics investigates the relationship between germline genetic variation and patient response to radiotherapy, including normal tissue toxicity and tumour radiosensitivity. Over the past decade, multiple genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) associated with increased risk of radiation-induced toxicity, such as fibrosis or proctitis [68,69]. These findings have opened the possibility of personalizing dose prescriptions based on genetic risk.

For example, SNPs in TGFβ1 and ATM genes have been associated with higher fibrosis rates in breast cancer patients undergoing adjuvant radiotherapy, suggesting that dose modulation or more frequent monitoring could reduce late toxicity [70,71]. Integration of radiogenomic data with clinical and dosimetric parameters has enabled development of predictive nomograms that can guide individualized treatment planning. Table 4 summarizes selected radiogenomic associations between specific genes or SNPs and observed radiotherapy toxicities across different cancer types.

Table 4
Selected radiogenomic associations with radiotherapy toxicity.

Gene/SNP	Cancer Type	Observed Toxicity
TGFβ1 (C-509T) [70,71]	Breast	Fibrosis
ATM (rs1801516) [69]	Prostate	Late rectal toxicity
XRCC1 (Arg399Gln) [68]	Head & Neck	Mucositis

5.2. Radiomics: imaging biomarkers for response prediction

Radiomics extracts high-dimensional quantitative features from imaging datasets (CT, MRI, PET) to capture tumour heterogeneity and microenvironmental characteristics. Studies over the past decade have demonstrated that radiomic signatures can predict tumour radiosensitivity, the likelihood of local recurrence, and toxicity risk to organs at risk [56].

For instance, in non-small cell lung cancer (NSCLC), texture-based radiomic features from pretreatment CT scans have been correlated with both local control and overall survival following stereotactic radiotherapy [72]. Similarly, PET radiomics has been explored to guide adaptive strategies in head and neck cancers, potentially identifying hypoxic subregions that may benefit from dose escalation.

5.3. Tumour microenvironment and radiosensitivity

Understanding the tumour microenvironment (TME) has been central to predicting radiotherapy outcomes. Hypoxia, immune infiltration, and stromal composition influence radiosensitivity. Over the last decade, hypoxia-targeted approaches (e.g., dose painting with IMRT or hypoxia-activated prodrugs) have entered clinical trials, aiming to escalate dose to radioresistant regions [73]. Additionally, studies integrating immune profiling with radiotherapy have demonstrated that tumours with pre-existing T-cell infiltration respond more favourably to treatment, highlighting the intersection between radiation and immunology [74].

5.4. DNA damage response and radiosensitization

Advances in understanding DNA repair pathways have enabled rational combinations of radiotherapy with targeted agents. PARP inhibitors, ATR inhibitors, and DNA-PK inhibitors can enhance tumour cell kill by exploiting defects in homologous recombination or non-homologous end-joining pathways. Preclinical and early-phase clinical studies have demonstrated feasibility in breast, ovarian, and head-and-neck cancers [23,75]. Table 5 highlights examples of targeted radiosensitizers under investigation, detailing their mechanisms of action, tumour types targeted, and current clinical development phases.

5.5. Immuno-radiotherapy combinations

The combination of radiotherapy with immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1, anti-CTLA-4) has been a major translational focus. Radiation can induce immunogenic cell death, upregulate antigen presentation, and modulate TME, potentially enhancing systemic anti-tumour immunity ("abscopal effect") [22].

Clinical trials in NSCLC, melanoma, and head-and-neck cancer have shown that combining radiotherapy with immunotherapy can improve local and distant tumour control, though optimal timing, fractionation, and patient selection remain areas of active research [78,79]. Fig. 2 schematically illustrates how combining radiotherapy with immunotherapy can enhance both local and distant tumour control by leveraging radiation-induced immune activation and systemic anti-tumour responses.

Table 5
Examples of targeted radiosensitizers under investigation.

Drug/Class	Mechanism	Tumour Type	Clinical Phase
Olaparib (PARP inhibitor) [75]	Inhibits DNA repair	Breast, ovarian	Phase I-II
AZD6738 (ATR inhibitor) [76]	Blocks ATR-mediated repair	Head & Neck	Phase I
NU7441 (DNA-PK inhibitor) [77]	Inhibits NHEJ	Glioblastoma	Preclinical

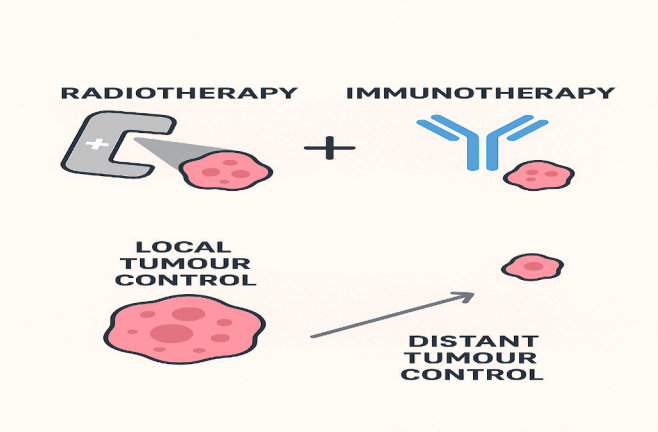

Fig. 2. Illustrates the interplay between Immuno-radiotherapy combination cancer treatment.

6. Radiation-induced cardiotoxicity

As survival after cancer treatment improves, late toxicities, particularly cardiovascular damage, have become increasingly important in gauging the long-term trade-offs of radiotherapy. Radiation-induced cardiotoxicity (RICT) encompasses a spectrum of pathologies which include pericarditis, coronary artery disease, myocardial dysfunction, valvular disease, arrhythmias, and late heart failure that may surface months to decades after thoracic irradiation [80–82].

6.1. Mechanisms and pathophysiology

RICT reflects the heart's heterogeneous radiosensitivity across substructures, including myocardium, coronary arteries, valves, pericardium, and the conduction system,so clinical syndromes vary depending on which regions receive dose. Mechanistically, early injury is commonly described as endothelial damage with oxidative stress and inflammatory signaling, producing microvascular dysfunction that can set the stage for later remodeling [83]. Over time, chronic injury is driven by progressive fibrosis and vascular pathology, including microvascular rarefaction and ischemic sequelae with downstream myocyte dysfunction/loss [84].

The downstream pathophysiology is substructure-specific. Radiation-associated coronary artery disease is widely attributed to radiation-related endothelial injury and accelerated atherosclerosis in the epicardial coronaries [85]. Myocardial injury is closely linked to microvascular damage and fibrotic remodeling rather than direct myocyte killing alone [84]. Valvular disease characteristically presents after latency with diffuse leaflet thickening, fibrosis, and calcification (often left-sided) [86]. Pericardial disease spans acute or delayed pericarditis/effusion and, years later, may progress to constrictive pericarditis through fibrotic thickening and calcification [87].

Fractionation matters because many cardiac endpoints behave as late-responding tissue effects with low α/β (reported as <6 Gy) implying that larger dose per fraction can increase late injury risk for a given physical dose distribution [88]. Concurrent cancer treatments such as anthracyclines, trastuzumab, or other chemotherapy with cardiotoxic potential augment risk through synergistic injury [89].

6.2. Risk factors

Multiple clinical and treatment-related factors modify risk. Key among these are radiation dose and volume, where the cumulative heart dose and the proportion of the heart or its critical substructures (such as left ventricle and left anterior descending artery) within high-dose regions increase risk. Risk increases in a roughly linear manner with

increasing mean heart dose in breast cancer, at approximately 7.4% per Gy [90,91]. Disease site strongly shapes cardiac risk because typical heart dose distributions differ by indication. In left-sided breast RT, modern techniques often achieve low-single-digit mean heart doses (commonly around ~2–3 Gy, though higher values occur depending on targets/technique), but dose to the left anterior descending (LAD) coronary artery is clinically salient and is increasingly treated as a key substructure constraint [92]. n lung cancer, heart exposure is highly dependent on tumour location and technique; systematic evidence shows wide variability in mean heart dose (including ranges extending into the 30–40+ Gy region across published regimens), with anterior cardiac substructures and coronary regions sometimes receiving high doses in centrally located or mediastinal-adjacent disease [93].

Fractionation and dose per fraction also play important roles, as larger fractions exceeding 2 Gy exacerbate late effects [89]. Laterality and target region significantly influence exposure, with left-sided breast irradiation, inclusion of internal mammary lymph nodes, or mediastinal and chest wall fields exposing more cardiac tissue [94]. Patient age and comorbidities further modify susceptibility, with younger age at exposure, existing cardiovascular disease, or risk factors such as hypertension, diabetes, hyperlipidemia, and smoking heightening risk. Time since exposure is also important, as many adverse events occur 10–30 years later [81].

6.3. Clinical evidence and dose-response relationships

A growing evidence base links specific dosimetric metrics to clinically meaningful cardiac endpoints. In breast cancer patients, for example, studies showed that for patients receiving trastuzumab, a heart V(25Gy) $\geq$ 3% was associated with significantly higher rates of cardiotoxicity compared to lower exposure (approx. 5.7% vs 1.5%) [95].

Expert panels and systematic reviews have proposed constraints: for whole breast adjuvant RT, “mean heart dose <2.5 Gy”, “mean left ventricle dose <3 Gy”, and constraints on volumes of LV or LAD receiving low to moderate doses (e.g., V5 LV <17%, V23 LV <5%, etc.) are suggested to reduce cardiac risk (DEGRO breast cancer expert panel) [96]. Table 6 summarizes disease-site-specific dose-volume constraints and associated cardiac endpoints.

6.4. Cardiac sparing & mitigation strategies

Several technical and treatment design strategies have been adopted or refined to limit cardiac toxicity without compromising oncologic outcomes. Breath-hold techniques, especially deep inspiration breath hold (DIBH), increase separation of the heart from chest wall and breast, thereby reducing mean heart dose and LAD exposure. Meta-analytic and dosimetric studies indicate DIBH can reduce heart dose by 20-70% in left-sided breast cancer compared to free breathing [101,102]. Advanced beam delivery techniques including IMRT, VMAT, and proton therapy allow more conformal treatments, reducing high-dose exposure to cardiac substructures [94,103]. Dose constraints for heart and substructures have become standard practice, with utilization of constraints not only for whole heart (mean heart dose, Vx) but for substructures such as left ventricle and LAD. For example, constraints like LAD Dmax less than 20 Gy or mean less than 10 Gy are commonly applied in partial breast settings [97]. Minimizing fraction size where feasible and ensuring careful planning for patients who will receive cardiotoxic systemic therapy such as trastuzumab simultaneously or sequentially represents another important mitigation strategy [104,105]. Cardio-oncology integration in modern practice increasingly incorporates structured cardiovascular risk assessment prior to radiotherapy, including baseline echocardiography, troponin and NT-proBNP biomarker measurement, and consultation with cardio-oncology specialists for high-risk patients. Surveillance protocols now recommend serial echocardiographic monitoring and biomarker assessment during and after treatment, particularly for patients receiving concurrent anthracyclines or anti-HER2 therapy. Coordination with systemic therapy teams allows for optimized sequencing of cardiotoxic agents and radiotherapy, with growing evidence supporting anthracycline completion before radiotherapy where feasible, and careful cardiac monitoring when concurrent treatment is necessary. This multidisciplinary approach integrates radiotherapy planning into a broader cardioprotective framework that extends beyond radiation dose optimization to encompass comprehensive cardiovascular risk management.

6.5. Gaps, challenges and future directions in cardiotoxicity mitigation

Despite increasingly refined dosimetric data, several gaps remain. Long-term clinical endpoints present a challenge, as many studies focus on surrogate markers such as imaging and biomarkers or early cardiac events, while data for outcomes like heart failure, valvular disease, or coronary events occurring 20 or more years post-treatment are limited in many populations. Substructure motion and dose tracking remain incompletely addressed, as the heart and its substructures move with respiration and the cardiac cycle, yet most planning is static. Emerging imaging approaches such as 5D-MRI workflows may allow tailored margins and dose constraints with motion included [106]. The interplay with systemic therapy presents another gap, as the combined effects of radiotherapy plus chemotherapy or targeted agents with known cardiotoxicity are not fully quantified in many settings, and these combinations may lower safe dose thresholds. The impact of hypofractionation on cardiac risk requires further investigation, as much dose-response data comes from conventional fractionation, and whether hypofractionated schedules have equivalent cardiac risk per biologically corrected dose remains under investigation [89]. Population diversity in existing studies also limits generalizability, as older studies often underrepresent women, people with comorbidities, or those from non-white ethnic backgrounds, making extrapolation of risk across populations challenging.

6.6. The role of AI in mitigating radiotherapy-induced cardiotoxicity

The heart is a complex, mobile organ with multiple radiosensitive

Table 6
Disease-site-specific cardiac dose-volume constraints and associated endpoints.

Disease Site	Critical Structure	Recommended Constraint	Associated Endpoint	Reference
Breast (left-sided)	Whole heart	Mean dose <2.5 Gy	Ischemic heart disease	[96]
Breast (left-sided)	Left ventricle	Mean dose <3 Gy, V5 <17%, V23 < 5%	Myocardial dysfunction, heart failure	[96]
Breast (left-sided)	LAD	Dmax <20 Gy (partial breast), mean < 10 Gy	Coronary artery disease	[97]
Hodgkin Lymphoma (mediastinal)	Whole heart	Mean heart dose <15 Gy *(QUANTEC-based)*	Coronary disease, valvular disease, heart failure	[98]
Lung cancer (anterior/ mediastinal)	Whole heart	V30 < 40% *(planning constraint used in modern cohorts)*	Pericarditis, coronary events	[99]
Oesophageal cancer	Pericardium; whole heart	Mean pericardial dose ~26 Gy; pericardium V30 ~46% *(risk threshold reported for pericardial effusion)*	Pericardial effusion (and broader cardiac toxicity)	[100]

substructures, and conventional planning methods often struggle to account for inter-observer variation in contouring, respiratory and cardiac motion, and the competing demands of tumour coverage versus organ sparing. AI offers a means of overcoming these challenges by integrating imaging, dosimetric, and biological data into predictive and adaptive frameworks.

One of the most immediate contributions of AI lies in improved segmentation of cardiac substructures. Deep learning algorithms trained on large, annotated datasets have demonstrated superior reproducibility in delineating the left ventricle, LAD artery, and atria compared to manual methods [10]. This precision enables planners to apply more reliable dose constraints to critical structures, reducing uncertainty in estimated mean heart and LAD doses. Early clinical studies suggest that when AI-assisted contouring **is** used, variability in heart substructure delineation decreases significantly, resulting in more consistent application of dose-sparing strategies [107].

AI also contributes to treatment plan optimization, where algorithms can balance target coverage with minimization of cardiac exposure. Reinforcement learning and knowledge-based planning models are increasingly capable of predicting the optimal achievable dose distribution for a given anatomy, often outperforming conventional inverse planning in sparing the heart without compromising tumour control [108]. This has relevance for left-sided breast cancer, mediastinal lymphoma, and thoracic tumours where the proximity of the heart presents significant planning challenges.

Beyond planning, AI has potential in predictive modeling of toxicity risk. Radiomics and machine learning approaches can extract quantitative features from planning CT or MRI scans that correlate with microvascular injury, perfusion abnormalities, or long-term cardiac events [109]. When integrated with serum biomarkers such as troponin and NT-proBNP in a multi-parametric approach, these models enable more precise cardiac risk stratification before treatment begins, supporting personalized dose de-escalation or selection of techniques such as deep inspiration breath hold or proton therapy. Importantly, these predictive tools can be updated continuously with post-treatment imaging and biomarker data, creating adaptive feedback loops for long-term surveillance.

Emerging research also suggests AI could enable real-time motion management by integrating cine-MRI or fluoroscopic imaging with deep learning models that track and predict cardiac and respiratory motion [110]. This capability could allow dynamic beam gating or adaptive modulation that spares moving cardiac substructures more effectively than static margins. Such innovations may be crucial for reducing inadvertent dose to the LAD and left ventricle, structures strongly implicated in long-term morbidity.

While AI applications are still maturing, early evidence indicates that their integration into radiotherapy workflows holds genuine promise for reducing the incidence of radiation-induced cardiotoxicity. Cross-referencing the AI applications described in Section 4.5, the same auto-contouring platforms (e.g., Limbus AI, MIM Contour ProtégéAI) and knowledge-based planning tools (e.g., RapidPlan) discussed for general workflow optimization can be extended specifically to cardiac substructure delineation and dose-volume optimization, reinforcing the narrative that AI-driven cardiotoxicity mitigation is tightly integrated with broader workflow innovation. Future research should focus on multi-institutional validation of AI models, integration of cardiac biomarkers into predictive algorithms, and transparent governance frameworks to ensure reproducibility and safety. As these systems evolve, they may redefine the balance between effective tumour control and preservation of long-term cardiovascular health, turning AI from a tool of convenience into a cornerstone of toxicity mitigation as illustrated in Fig. 3.

7. Future directions and emerging trends in radiotherapy

The next decade of radiotherapy promises profound transformation driven by the convergence of technology, biology, and clinical innovation. Among the most promising developments is the translation of ultra-high dose-rate radiotherapy, commonly referred to as FLASH. Preclinical evidence demonstrates that FLASH irradiation can spare normal tissues while maintaining tumour control, fundamentally altering the therapeutic window of radiation [50]. This approach challenges long-standing assumptions about dose fractionation and normal tissue tolerance. Nevertheless, clinical translation faces substantial technical hurdles. Delivering FLASH to deep-seated tumours requires sophisticated beam-shaping technologies, and rigorous dosimetric verification is essential to ensure reproducibility and safety. Beyond physical delivery, the biological underpinnings of FLASH, hypothesized to involve oxygen depletion dynamics and altered free radical chemistry remain incompletely understood. As a result, cautious yet deliberate clinical trials are underway, aimed at elucidating both efficacy and mechanistic principles, with early feasibility studies in superficial malignancies providing the first human data.

Concurrently, AI is poised to reshape radiotherapy practice beyond workflow automation into the realm of real-time treatment personalization. Whereas current applications primarily focus on auto-contouring

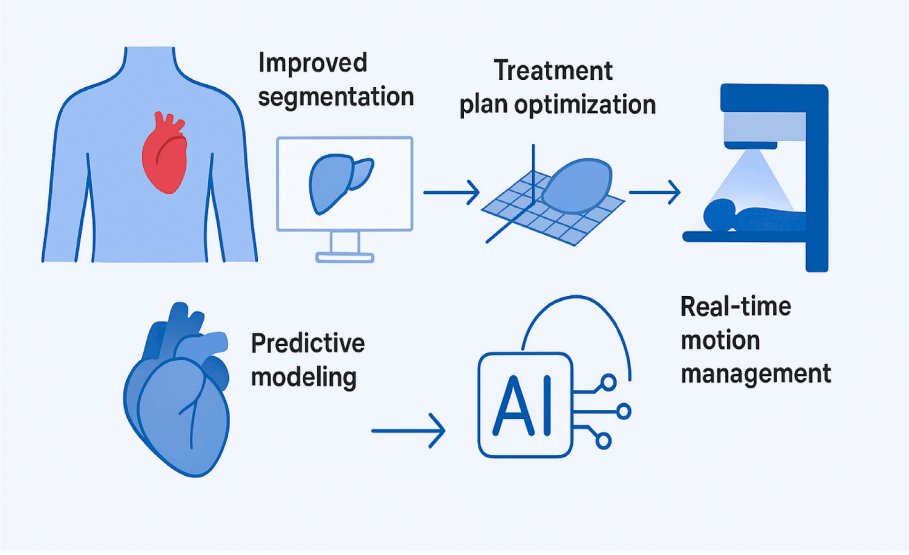

Fig. 3. Schematically illustrates how AI integrates segmentation, planning, prediction, and motion management to reduce heart dose.

and plan optimization, emerging AI-driven adaptive radiotherapy platforms promise to integrate imaging, genomics, and functional biomarkers into on-table decision-making. For instance, predictive models may anticipate tumour volumetric changes or organ motion, allowing automated replanning without human intervention. Coupled with radiomic and radiogenomic data, such systems could adjust dose distributions dynamically, tailoring therapy not only to anatomical changes but also to individual tumour biology and patient-specific toxicity risk. This fusion of computational analytics with adaptive delivery heralds a new paradigm of precision radiotherapy that is both predictive and responsive.

A central theme in future radiotherapy is biologically informed personalization. Integrating radiogenomic and radiomic insights enables clinicians to move beyond population-based protocols toward individualized treatment. For example, genetic variants linked to radiosensitivity, such as SNPs in TGFβ1 or ATM, could inform dose modulation strategies, reducing the risk of late toxicity in susceptible patients [69,71]. Meanwhile, radiomics allows extraction of high-dimensional imaging features that reflect tumour heterogeneity, hypoxia, and microenvironmental composition, providing predictive insight into both local control and toxicity outcomes [56,72]. The combination of these approaches supports a future in which fractionation, dose escalation, and adaptive strategies are personalized on both biological and anatomical grounds.

The role of radiotherapy in systemic disease management is also expanding. The intersection with immunotherapy exemplifies this trend. Radiotherapy not only achieves local tumour control but also modulates the tumour microenvironment, promoting antigen release, dendritic cell activation, and T-cell priming, a phenomenon exploited in the so-called abscopal effect [22]. Clinical trials combining checkpoint inhibitors with radiotherapy in NSCLC, melanoma, and head-and-neck cancer indicate enhanced systemic response rates, although optimal sequencing, dose fractionation, and patient selection remain active areas of research [78]. Similarly, the combination of radiotherapy with targeted DNA repair inhibitors, such as PARP or ATR inhibitors, holds promise in radiosensitizing tumours with specific genomic vulnerabilities, potentially converting otherwise resistant tumours into curable ones [75].

From a health-economics and policy angle, radiotherapy innovation is increasingly constrained by value-for-money and access. Technologies like proton therapy and MR-linacs can reduce normal-tissue dose, but their capital intensity and workflow complexity sharpen the question of incremental benefit versus scalable photon alternatives: multi-room proton centers have long been costed in the ~$150–200M range to build [46], while MR-linac acquisition is commonly cited as >$7.5M (and often around €10M in European implementations), before facility and staffing requirements [111]. In contrast, cost-effectiveness work around ultra-hypofractionation (e.g., FAST-Forward breast RT) indicates system-level efficiency gains with fewer visits and lower delivery costs, supporting the argument that fraction reduction can free capacity and reduce per-patient costs even without new platform investment [112]. However, real-world adoption and "value" remain health-system dependent, with uptake patterns shaped by reimbursement, workforce, and infrastructure differences [113].

Equity is the harder constraint: global analyses show a severe radiotherapy shortfall, with >90% of people in low-income countries lacking access to radiotherapy and substantial unmet need across LMICs more broadly [114]. Addressing this requires pragmatic policy frameworks that extend beyond equipment procurement to include workforce development, training pipelines, and sustainable operational models. AI-supported remote treatment planning and cloud-based quality assurance represent promising avenues for democratizing access to expert-level care, allowing resource-limited centers to benefit from automated contouring, plan optimization, and real-time QA oversight without requiring on-site specialists. International collaboration models that link high-income centers with LMIC institutions via tele-radiotherapy networks are emerging but remain underutilized. Policy interventions must prioritize investment in radiotherapy infrastructure as cost-effective means of reducing global cancer mortality, as emphasized by the Lancet Oncology Commission [11].

Overall, the future of radiotherapy is defined by integration. Ultra-high dose-rate modalities like FLASH, AI-driven adaptive planning, biologically informed personalization, and synergistic combinations with systemic therapy converge to redefine the boundaries of tumour control and normal tissue preservation. Yet, realizing this vision will demand not only technological innovation but also rigorous translational research, multidisciplinary collaboration, and a commitment to global equity. Conceptually, this emerging landscape can be summarized in Fig. 4, which illustrates the intersection of technological innovation, biological personalization, and systemic integration, highlighting how these domains collectively shape the next generation of radiotherapy.

8. Limitations of this review

This narrative review has several important limitations that should be acknowledged. First, as a narrative rather than systematic review, it did not employ PRISMA methodology or conduct formal risk-of-bias assessment across all included studies. While we prioritized high-quality randomized controlled trials, prospective cohorts, and authoritative guidelines, the qualitative synthesis approach may introduce selection bias, and findings should be interpreted recognizing this methodological constraint.

Second, the evidence base for several emerging technologies, including FLASH radiotherapy, biologically-guided radiotherapy, and some AI applications, remains limited, with much data derived from early-phase trials, preclinical models, or single-institution experiences. Long-term clinical outcome data, particularly for cardiotoxicity endpoints 20+ years post-treatment, are sparse for newer modalities and hypofractionated regimens, limiting our ability to draw definitive conclusions about late effects.

Third, the review's scope encompasses a broad range of technologies, disease sites, and biological insights, which necessarily precludes exhaustive coverage of any single domain. Specific topics such as brachytherapy, pediatric-specific protocols, and region-specific practice variations receive limited attention. Additionally, cost-effectiveness analyses and health economics data remain heterogeneous and often institution-specific, limiting generalizability of economic conclusions.

Fourth, much of the cardiotoxicity dose-response data derives from conventionally fractionated regimens in predominantly white, high-income populations. Extrapolation to hypofractionated schedules, diverse ethnic groups, and resource-limited settings requires caution, as population-specific risk factors and baseline cardiovascular health may

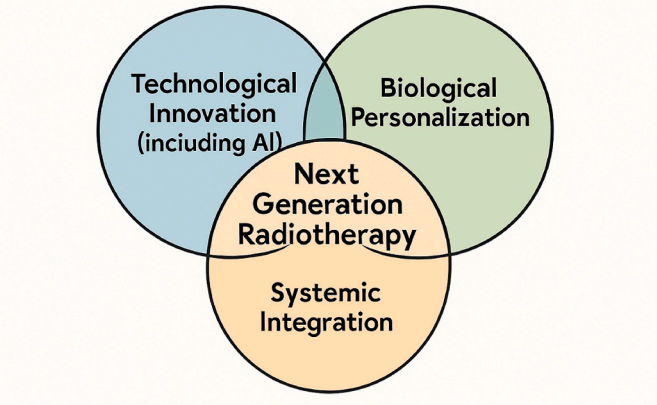

Fig. 4. Illustrates the intersection of technological innovation including AI, biological personalization, and systemic integration.

significantly modify outcomes.

Finally, the rapidly evolving nature of AI applications, regulatory landscapes, and clinical trial data means that some content may become outdated between manuscript preparation and publication. Readers are encouraged to consult contemporary clinical trial registries and regulatory updates for the most current information on emerging technologies and guidelines.

9. Conclusion

The past decade has witnessed a remarkable evolution in radiotherapy, transitioning from conventional, largely anatomical approaches to highly precise, biologically informed, and computationally integrated therapies. Technological advances, including image-guided radiotherapy, MR-linac platforms, proton and particle therapy, biologically-guided delivery systems, radiopharmaceutical therapy, and emerging modalities such as FLASH irradiation, have substantially enhanced the precision, safety, and efficacy of treatment. These innovations have not only allowed dose escalation to tumours while sparing normal tissue but have also enabled adaptive workflows that respond dynamically to anatomical and physiological changes, fundamentally redefining the therapeutic ratio. Concurrently, the integration of biological insights, encompassing radiogenomics, radiomics, tumour microenvironment profiling, and DNA damage response mechanisms, has shifted radiotherapy toward personalized care. By incorporating patient-specific genetic risk factors, tumour heterogeneity, and functional imaging biomarkers into clinical decision-making, clinicians can now tailor fractionation, dose, and treatment sequencing to optimize outcomes. The synergy of radiotherapy with systemic agents, including immunotherapies and targeted DNA repair inhibitors, further expands the potential of radiotherapy from a purely local modality to a contributor to systemic tumour control, opening new avenues for curative-intent treatment in previously challenging clinical scenarios.

Amid these gains, recognition of late cardiovascular toxicities has underscored the need to balance efficacy with survivorship. Radiation-induced cardiotoxicity, encompassing coronary disease, myocardial dysfunction, valvular injury, and arrhythmias, represents a critical challenge that demands integration of cardiac-sparing planning techniques, motion management, AI-driven risk prediction, and multidisciplinary cardio-oncology care. Advances in deep inspiration breath-hold techniques, cardiac substructure contouring, and multi-parametric biomarker integration represent meaningful progress, yet continued research is needed to refine long-term outcome data, understand hypofractionation impacts, and develop population-specific risk models.

Artificial intelligence promises to transform practice by integrating biological, imaging, and dosimetric data into adaptive frameworks, potentially enabling real-time personalization while reducing cardiac risk. However, regulatory frameworks ensuring human-in-the-loop oversight, algorithmic transparency, and legal liability clarity remain essential to responsible clinical deployment. At the same time, addressing global disparities in access to modern radiotherapy remains a pressing challenge. Workforce shortages, training deficits, and infrastructure gaps in low- and middle-income countries limit the reach of technological innovation. Policy interventions must prioritize cost-effective strategies including ultra-hypofractionation, AI-supported remote planning, cloud-based quality assurance, and international tele-radiotherapy collaboration to extend modern radiotherapy beyond high-income settings.

The decade ahead must focus on translating emerging technologies such as FLASH irradiation through rigorous clinical trials, strengthening cardio-oncology integration and long-term surveillance programs, and ensuring equitable dissemination of innovations through pragmatic adoption frameworks and supportive health policy. By aligning precision with safety and access, radiotherapy can continue its evolution into a discipline that is not only more effective but also safer and globally relevant.

CRediT authorship contribution statement

Emmanuel O. Oisakede: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Babajide F. Ajeyomi:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Olawunmi O. Oyedeji:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Oluwakemi Jumoke Bello:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Claret Chinenyenwa Analikwu:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **David B. Olawade:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation.

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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