Radiotherapy toxicities: mechanisms, management, and future directions

Ioannis I Verginadis, Deborah E Citrin, Bonnie Ky, Steven J Feigenberg, Alexandros G Georgakilas, Christine E Hill-Kayser, Constantinos Koumenis, Amit Maity, Jeffrey D Bradley, Alexander Lin

Lancet 2025; 405: 338–52

Published Online January 16, 2025 https://doi.org/10.1016/S0140-6736(24)02319-5

Department of Radiation Oncology (I I Verginadis PhD, Prof S J Feigenberg MD, Prof C Koumenis PhD, Prof J D Bradley MD, Prof A Lin MD, C E Hill-Kayser MD)**, and Department of Cardiovascular Medicine** (Prof B Ky MD)**, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA** (Prof D E Citrin MD)**; Department of Physics, School of Applied Mathematical and Physical Sciences, National Technical University of Athens, Athens, Greece** (Prof A G Georgakilas PhD)**; Cancer Center, Children's Hospital of Philadelphia, Philadelphia, PA, USA** (C E Hill-Kayser MD)**; Department of Radiation Oncology, University of Utah Health, Salt Lake City, UT, USA** (Prof A Maity MD)

Correspondence to: Dr Ioannis I Verginadis, Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-156, USA **vioannis@pennmedicine.upenn.edu**

For over a century, radiotherapy has revolutionised cancer treatment. Technological advancements aim to deliver high doses to tumours with increased precision while minimising off-target effects to organs at risk. Despite advancements such as image-guided, high-precision radiotherapy delivery, long-term toxic effects on healthy tissues remain a great clinical challenge. In this Review, we summarise common mechanisms driving acute and long-term side-effects and discuss monitoring strategies for radiotherapy survivors. We explore ways to mitigate toxic effects through novel technologies and proper patient selection and counselling. Additionally, we address policies and management strategies to minimise the severity and impact of toxicity during and after treatment. Finally, we examine the potential advantages of emerging technologies and innovative approaches to improve conformity, accuracy, and minimise off-target effects.

Introduction

Radiotherapy has been an effective cancer treatment for more than a century. The origins of radiotherapy can be traced back to the late 19th century, when Wilhelm Conrad Roentgen (later awarded the first Nobel Prize in Physics in 1901) accidentally discovered x-rays while using a tube invented by William Crookes.[1] This finding provided the groundwork for the use of ionising radiation in medicine, laying the foundation for the development of radiotherapy as a therapeutic technique.

Recent technical advancements in radiotherapy have allowed for better delivery of therapeutic doses of radiation to areas of cancer involvement, while minimising the dose delivered to the surrounding healthy organs at risk of off-target effects. This improvement has been accomplished through various advances implemented at different points in the therapeutic process. Before treatment begins, diagnostic imaging (such as CT, PET, and MRI) can be used to identify and outline tumours to target during radiotherapy treatment. In the late 1980s to early 1990s, the incorporation of CT scans allowed for the reconstruction of tumours and healthy organs in three dimensions, and thereby led to the development of three dimensional (3D) spatial radiation planning (3D conformal radiotherapy). This advance allowed for multiple radiation beams to be used, conforming radiation as much as possible to the tumour and avoiding healthy organs. Subsequent advances, with further confinement of high-dose radiation by small beamlets of varying intensity (intensity-modulated radiotherapy), have resulted in improved patient outcomes through toxicity reduction.[2] Another means to reduce the dose of radiation to which healthy tissues are exposed became available with the advent of particle therapy. The physical properties (eg, mass and charge) of the particles used in particle therapy, a form of external beam radiotherapy (using, for example, protons, carbon ions, or helium ions), have the benefit of inducing the Bragg peak effect, whereby the majority of the radiation dose is deposited at a specific depth corresponding to the tumour location. The Bragg peak effect results in a minimal dose delivery to healthy tissues around the tumour, which can help to reduce the risk of adverse events. During daily treatment, imaging can be done by the radiotherapy unit (image-guided radiotherapy) to visualise anatomy, ensuring optimal accuracy and precision throughout treatment. Image-guided radiotherapy thereby allows for any required adaptation of the radiotherapy plan (adaptive radiotherapy) based on changes in patient anatomy during treatment (such as from tumour response).

Currently, radiotherapy is indicated for more than 50% of all patients with cancer.[3] Although the benefits of radiotherapy are well established, even the most advanced

Search strategy and selection criteria

We searched PubMed, Scopus, and MEDLINE using the search terms "radiation-induced adverse events", "radiation toxicity", "management of toxicities", "monitoring of side effects", or "acute and late side effects" in titles or abstracts. In addition, we searched for combinations of the terms "radiotherapy and immunotherapy", "stereotactic body radiation therapy and immunotherapy", "abscopal effect radiation", "FLASH", "proton therapy and toxicity", "MRI and radiation toxicity", "adaptive radiation", "temporal and spatial fractionation", "liquid biopsy and biomarkers", and "artificial intelligence". Searches were done on multiple dates between Aug 10, 2023, and Sept 28, 2024, with a final update on Oct 8, 2024. Relevant articles published in English between April 7, 1934, and Aug 30, 2024 were identified. Abstracts and reports from meetings were included only if they were directly related to previously published work. All authors had access to the full text of all selected publications. Due to the large number of eligible publications, the final selection of references for this Review was based on the most recent and relevant studies that offered the highest combined level of evidence.

technologies cannot completely prevent exposure of healthy tissues to clinically significant incidental doses of radiation, which can lead to considerable long-term morbidity and adversely affect patients' quality of life. Depending on the treatment site and the delivered dose of radiotherapy, various radiotherapy-induced toxic effects across different organs have been identified (figure 1, table),[4,5] including a low but measurable risk of radiation-induced malignancy among long-term survivors[42] (for example, in a single-site study in the USA,[43] 8·3% of children who received radiotherapy for a primary tumour developed a secondary malignancy, mainly within the original site of radiotherapy). Among adults, women who receive breast radiotherapy and men who receive prostate radiotherapy comprise patient populations for whom radiotherapy is a commonly used treatment with long-term follow-up. Among women receiving breast radiotherapy, 13·0% developed a secondary malignancy, of which 3·4% were attributable to radiotherapy.[44] In men treated for prostate cancer, those who received radiotherapy had a 1·2% greater incidence of a second primary cancer than those treated without radiotherapy.[45]

In this Review, we broadly discuss the mechanisms of radiotherapy toxicity and explore key clinical considerations related to radiotherapy, including monitoring of late side-effects, strategies for optimisation of patient selection for radiotherapy, and methods for the management of toxic effects without treatment interruption. Finally, we explore the latest innovative technologies aiming to improve conformity and accuracy while minimising healthy tissue toxicity.

Mechanisms

Radiotherapy can cause both acute and late toxic effects (figure 2). The acute (early) reactions are thought to be due to damage of cells with a rapid turnover rate, such as those in the epithelium of the gastrointestinal tract, oral mucosa, and skin (figure 2). This damage can lead to side-effects such as diarrhoea, mucositis, oesophagitis, and desquamation, but is often reversible, resulting in no permanent sequelae. By contrast, late effects, which are seen in tissues where cells divide slowly, are often more consequential and not readily reversible.

Although early toxicity from radiotherapy is primarily attributed to the death of rapidly dividing cells, accumulated evidence suggests that the microbiome is closely associated with the development and prevention of various radiation-induced toxic effects. Specifically, the oral and gut microbiome might modulate the effects of radiation on oral mucositis in patients receiving treatment to the head and neck region, or on enteritis for those receiving abdominal or pelvic radiation.[46,47] These findings suggest that microbiome-targeted therapies, such as probiotics or prebiotics, could improve patient outcomes by mitigating the adverse events of radiotherapy. Radiation-induced lymphopaenia, (which appears dependent on number of fractions and field size) is also an important concern, especially in the era of immunomodulatory drugs and radiotherapy combinations.[48] Much attention is now being given to the effective dose to immune cells (amount of radiation dose received by immune cells as they circulate through the body during radiotherapy treatments).[49,50] A high effective dose to immune cells is associated with severe lymphopaenia, leading to worse clinical outcomes in oesophageal and lung cancer, suggesting that the immune system should also be considered to be an organ at risk. A high effective dose also correlates with increased morbidity, often manifested through acute hospitalisations, which could be attributed to the lysis of circulating lymphocytes, which might lead to reduced anti-tumour activity.[51]

The toxic effects on which this Review focuses are mostly due to cell death, which can eventually lead to organ dysfunction. Historically, these were termed deterministic effects, but are now sometimes referred to as tissue reactions.[52,53] Radiation is also associated with stochastic effects, which can result from DNA mutations and lead to a second malignancy. These two broad categories—tissue reactions and stochastic effects—are characterised by very different features. The deterministic nature of acute and most late tissue reactions means that these are directly related to the dose received; higher doses lead to more severe and immediate side-effects, such as skin redness or hair loss, with a clear dose threshold below which these effects do not occur. By contrast, the relationship between dose and some specific effects, such as secondary

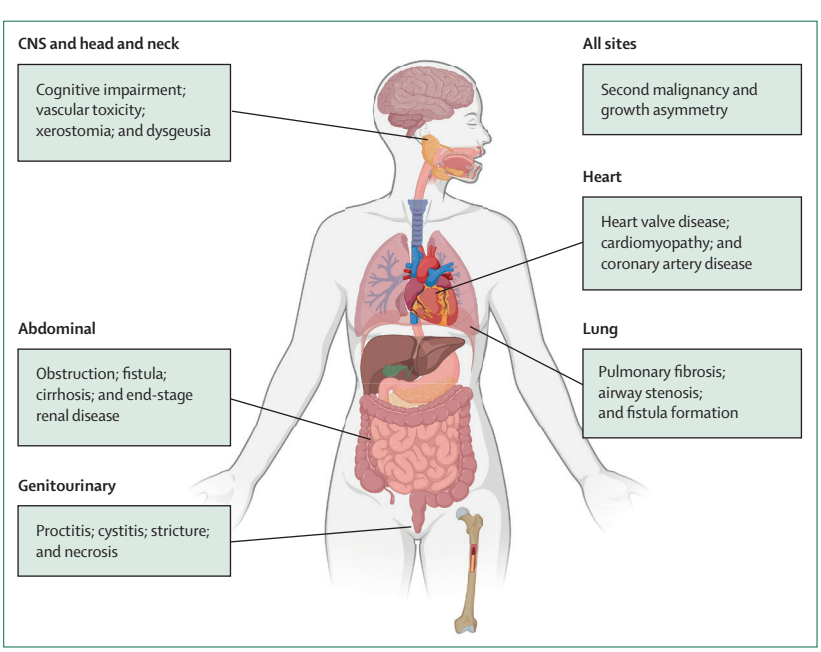

Figure 1: **Toxic effects of radiotherapy by site**
General overview of the most common long-term toxic effects of radiotherapy arising in different regions of the body. Figure created with BioRender.com.

	Long-term adverse events	Expected incidence rates (%)*	Potential management strategies
Abdomen			
Bile ducts	Biliary stenosis	4% (grade 1)[8]	Limit dose when treating hepatic region with SBRT to 40·0 Gy over 5 fractions[8]
Liver	Radiation-induced liver disease	<5% (dependent on pre-existing liver disease)[9]	Conventionally fractionated radiotherapy: limit average dose to whole liver to ≤28·0 Gy (for primary liver cancer) or ≤30·0 Gy (for liver metastases).[10] SBRT (3–6 fractions): limit average dose to whole liver to <20·0 Gy (for primary liver cancer) or <18·0 Gy (for liver metastases);[10] symptomatic management, diuretics, and paracentesis
Kidney	Renal dysfunction	<5%[9]	Limit mean radiotherapy dose to both kidneys to <15·0 Gy; limit volume receiving 12·0 Gy to <55%, volume receiving 20·0 Gy to <32%, volume receiving 23·0 Gy to <30%, and volume receiving 28·0 Gy to <20%;[9] medical management of hypertension and electrolyte abnormalities; dialysis for end-stage renal disease
Small intestine	Enteritis, obstruction, and fistula	Obstruction: 0·8–13·0%; fistula: 0·6–4·8%[11,12]	Limit volume of small intestine receiving 15·0 Gy to <120 cc;[9] symptomatic management: low-fibre diet, probiotics, hyperbaric oxygen, and surgery
Stomach	Ulceration	<7%[9]	Limit volume of stomach receiving 45·0 Gy to ≤2 cc[13]
Stomach	Perforation	<2%[14]	Limit maximum dose to <50·0 Gy[14]
Bone, skin, and soft tissue			
Bone	Fracture	0·6% (<50·0 Gy) and 7% (>60·0 Gy)[15]	Limit maximum dose to bone to ≤50·0 Gy; if treating with high-dose radiotherapy, limit maximum dose to bone to <60·0 Gy[15]
Lymphatic system	Lymphoedema	In the neck (with high-dose direct irradiation): 75%;[16] in the arm (after radiotherapy for breast cancer): 6–18%[17]	Limit the extent and volume of lymphatic regions that require both surgical resection and radiotherapy; physical decongestive lymphoedema therapy
Soft tissue	Fibrosis	In the neck (with high-dose direct irradiation): 74%;[18] in the breast: 5% (grade 2 or higher)[19]	Limit the extent and volume of soft tissues that require both surgical resection and radiotherapy; physical therapy (eg, exercise, stretches)
CNS			
Brain	Symptomatic necrosis	<20% (with high-dose direct irradiation)[9]	Limit maximum dose to <60·0 Gy;[9] with stereotactic radiosurgery, limit volume receiving 12·0 Gy to <10 cc[9]
Brainstem	Permanent cranial neuropathy or necrosis	<5%[9]	Limit brainstem dose to ≤59·0 Gy to 1–10 cc of brainstem or <64·0 Gy (point dose <1 cc of brainstem);[9] with stereotactic radiosurgery, limit maximum dose to brainstem to <12·5 Gy[9]
Cochlea	Sensorineural hearing loss	<30% (with high-dose irradiation close to the organ)[9]	Limit mean dose to cochlea to ≤45·0 Gy (conventional fractionated radiotherapy) or ≤14·0 Gy (stereotactic radiosurgery)[9]
Cochlea	Tinnitus	11·6%[20] (grade ≥2)	Limit mean dose to ≤32·0 Gy[20]
Eye (lens)	Cataracts	5%[21]	Limit maximum dose to lens to <10·0 Gy[21]
Eye (retina)	Retinopathy leading to vision loss	5%[21]	Limit maximum dose to retina to <45·0 Gy[21]
Optic nerve and chiasm	Optic neuropathy leading to vision loss	<3%[9]	Limit maximum dose to optic nerves or chiasm to <55·0 Gy;[9] with stereotactic radiosurgery, limit maximum dose to optic nerves or chiasm to <12·0 Gy[9]
Pituitary gland	Hypopituitarism	37%[22] (with high-dose irradiation to the anterior cranial skull base)	Limit pituitary dose according with specific hormone or dysfunction:[23] 18·0 Gy for growth hormone deficiency or central precocious puberty; 30·0 Gy for follicle-stimulating, luteinising, thyroid stimulating, adrenocorticotropic hormone; 50·0 Gy for hyperprolactinaemia
Spinal cord	Myelopathy	<1%[9]	Limit maximum dose to spinal cord to <50·0 Gy;[9] with stereotactic radiosurgery or SBRT, limit maximum dose to spinal cord to <13·0 Gy (stereotactic radiosurgery) or <20·0 Gy (3 fraction SBRT)[9]
Head and neck			
Brachial plexus	Plexopathy	1–2%[24]	Limit median dose to ≤69·0 Gy†;[25] with stereotactic radiosurgery or SBRT, limit max dose to† 17·5 Gy (stereotactic radiosurgery), 24·0 Gy (3 fraction SBRT), 27·2 Gy (4 fraction SBRT), or 32·0 Gy (5 fraction SBRT)[25]
Carotid artery	Carotid stenosis and stroke	Stenosis: 29%; stroke (with high-dose direct irradiation): 5%	Screening carotid ultrasounds, screening for dysautonomia, and optimal management of cardiovascular risk factors (blood pressure)
Lacrimal glands	Xerophthalmia	0–19% (with average dose to lacrimal gland of <30·0 Gy *vs* 30·0–45·0 Gy)[27]	Limit average dose to lacrimal gland to <30·0 Gy
Larynx	Voice changes, aspiration, and oedema	<20% (with high-dose direct irradiation)[9]	When radiating close to the larynx (but not directly), limit mean dose to larynx to <40·0 Gy
Mandible	Osteoradionecrosis	3%[28]	For prevention, maintenance of dental health and hygiene; prescription fluoride (for patients with xerostomia); surgical debridement or resection
Parotid gland	Xerostomia	32% (grade 2–3, with high-dose irradiation close to the organ)[29]	Limit average dose to <25·0 Gy to the combined parotid glands or <20·0 Gy to a single parotid gland;[9] dietary modifications (avoidance of dry, starchy foods) and pharmacological treatments (salivary stimulants or substitutes and lubricants)

(Table continues on next page)

	Long-term adverse events	Expected incidence rates (%)*	Potential management strategies
(Continued from previous page)			
Pharynx (pharyngeal constrictors)	Symptomatic dysphagia or aspiration	4% (grade 3–4)[29]	Limit average dose to <50·0 Gy to the pharyngeal constrictors;[9] evaluation and rehabilitation with speech and swallow therapists
Thyroid gland	Hypothyroidism	36% (with high-dose irradiation close to the organ)[30]	Limit volume of thyroid gland receiving 50·0 Gy to <50%;[31] limit average dose to thyroid gland to <55·0 Gy[31]
Pelvis			
Bladder	Bladder dysfunction (frequent urination, dysuria, haematuria, and reduction in capacity)	<6% (grade ≥2)[9]	For bladder cancer treatment, limit maximum dose to bladder to <65·0 Gy;[9] for prostate cancer treatment (conventional fractionated radiotherapy), limit the percentage of the bladder receiving 65·0 Gy to ≤50%, 70·0 Gy to ≤35%, 75·0 Gy to ≤25%, 80·0 Gy to ≤15%;[9] for prostate cancer treatment (hypofractionated radiotherapy), limit the percentage of the bladder receiving the percentage of the total prescribed radiotherapy dose to <5% for 100% of the prescribed dose or <50% for 68% of the prescribed dose[32]
Penile or urethral bulb	Severe sexual dysfunction	<35% (with high-dose irradiation close to the organ)[9]	For conventional fractionated radiotherapy, limit the percentage of the bulb receiving 50·0 Gy to ≤50% or 60·0 Gy to ≤10%;[32] for hypofractionated radiotherapy, limit the percentage of the bulb receiving the percentage of the total prescribed radiotherapy dose to <10% for 81% of the prescribed dose or <50% for 68% of the prescribed dose[32]
Rectum	Rectal dysfunction	<15% (grade 2); <10% (grade 3, with high-dose irradiation close to the organ)[9]	With conventional fractionated radiotherapy, limit the percentage of the rectum receiving 50·0 Gy to <50%, 60·0 Gy to <35%, 65·0 Gy to <25%, 70·0 Gy to <20%, or 75·0 Gy to <15%;[9] with hypofractionated radiotherapy, limit the percentage of the rectum receiving 28·0 Gy to ≤45%, 32·0 Gy to ≤35%, or 38·4 Gy to ≤15%;[33] medical management with stool softeners, fibre, sucralfate enemas, and glucocorticoid suppositories for mild proctitis, and ablative approaches (coagulation), formalin, hyperbaric oxygen, and surgery for moderate to severe proctitis
Ovary or testes	Infertility	Variable due to possible multiple contributing factors (eg, chemotherapy), but common even after low-dose exposure of ovaries or testes to radiotherapy	Fertility preservation before radiation and assisted reproduction (Survivorship Guidelines)
Vagina	Stenosis, necrosis, and fistula	1–15% (depending on radiotherapy technique and dose)[34]	Vaginal dilation, vaginal oestrogen, and surgical repair for vaginal fistula[34]
Thorax			
Oesophagus	Fistula and stenosis	Fistula (with chemoradiation for non-small-cell lung cancer): <1% (grade 5);[35] stenosis: 2% (at 50·0 Gy or less) to 15% (at >60·0 Gy)[36]	Limit max dose to oesophagus to <50·0 Gy
Heart	Cardiovascular events (eg, coronary disease, valvular dysfunction, heart failure, pericardial disease, and arrythmia)	23–32% (with high-dose irradiation close to the organ)[37]	Limit mean dose to heart to <20·0 Gy;[38] limit volume of left anterior descending artery receiving 15·0 Gy to <10%[39] and volume of left ventricle receiving 15·0 Gy to <1%[39]
Lung	Pneumonitis	12% (grade 1–2); <1% (grade ≥3, with high-dose direct irradiation)[40]	With conventional radiotherapy, limit volume of lung receiving 20·0 Gy to ≤40% and mean lung dose to ≤20·0 Gy†[25]
Lung	Fibrosis	10% (grade 1–2, with high-dose direct irradiation)[40]	Limit dose to <30 Gy[41]

Expected incidence rates are for the setting of curative-intent radiotherapy (definitive or adjuvant), unless also inclusive of treatment with SBRT or stereotactic radiosurgery as a management strategy. Toxic effects for which a specific grade is not listed are generally assessed by presence (yes vs no), do not have dedicated grading systems, or reliable data to estimate incidence are not available. For toxic effects with listed grades, these generally reference rates from published randomised controlled trials. SBRT=stereotactic body radiotherapy. *Before 1985, the radiotherapy literature used inconsistent terminology to report toxicity. From 1985 to 2000, toxicity was reported using the criteria as defined by the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer.[6] Since 2000, toxicity has been graded according to the Common Toxicity Criteria.[7] †National Comprehensive Cancer Network Clinical Practice Guidelines.

Table: **Brief summary of long-term adverse events associated with radiotherapy by affected organs or sites**

malignancies or genetic mutations, is stochastic. Therefore, these effects occur randomly, with the probability increasing with the dose, but without a specific threshold. Of note, late effects are generally absent at low radiation doses and many confounding factors, such as systemic therapy, can influence the occurrence of late toxic effects. Even low doses can potentially cause secondary malignancies because a mutation in a single gene could lead to cancer, but the risk is proportional to the dose received. With the increasing use of radiotherapy in the setting of multimodal therapy (which includes immunotherapy, drug-antibody conjugates, and biologically targeted agents), some adverse events can occur even with low doses of radiotherapy used in combination with other therapies (compared with higher doses of radiotherapy used alone). For example, stereotactic radiosurgery followed by immunotherapy can increase the risk of late

For more on the **Survivorship Guidelines** see http://www.survivorshipguidelines.org/

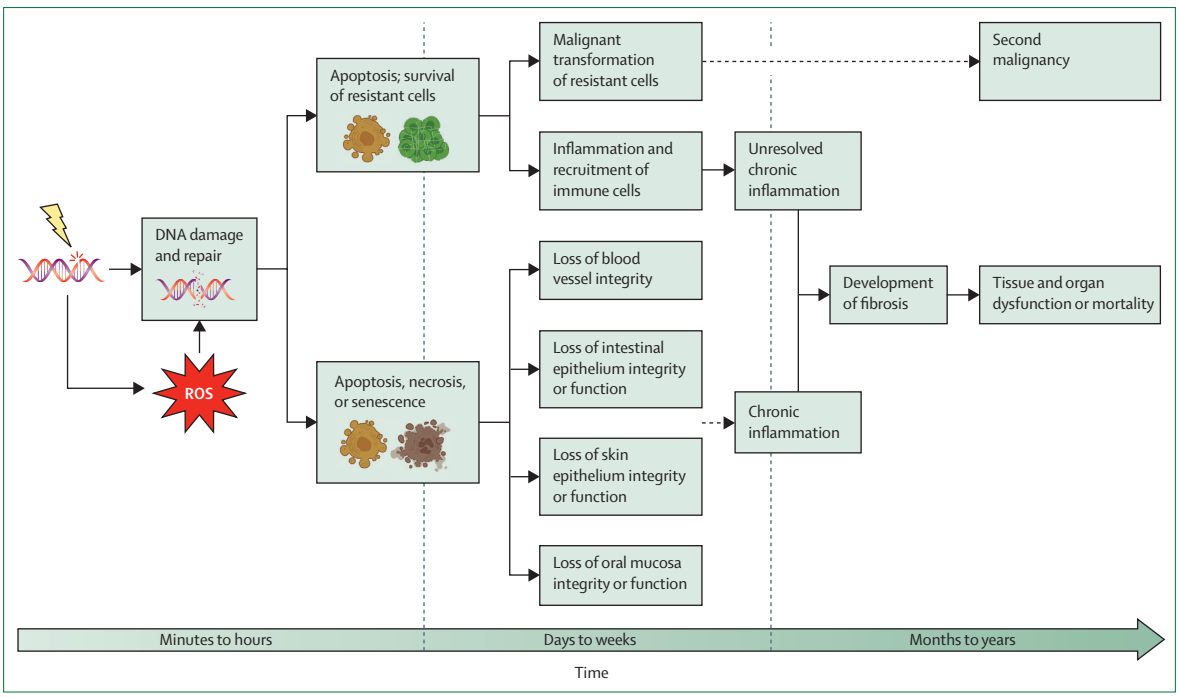

Figure 2: **Timeline of acute and late adverse events after radiotherapy**
Radiotherapy causes DNA damage and triggers an inflammatory response in which cells attempt to repair the damage. If the repair is insufficient, cells can undergo senescence or death, leading to various acute and late adverse events. Residual DNA damage in tissue stem cells can lead to malignant transformation and second cancers. Typically, long-term adverse events are irreversible, and limits to radiation doses are necessary to prevent these events. Figure created with BioRender.com.

brain necrosis. The cumulative effects of multiple treatments on healthy tissue response should therefore be considered when patient treatment is planned.

Many early effects can be explained by the target cell hypothesis, in which specific cell types are destroyed by radiation, but the pathophysiology of late injury is much more complicated. Late injury could involve both the loss of parenchymal cells and vascular endothelial cells,[54] potentially explaining effects such as hypoxia and necrosis. Although acute effects are not generally correlated with late effects, consequential late effects can arise from a persistent early effect. Consequential late effects are hypothesised to result from the depleted stem-cell population falling below the required amount needed for tissue regeneration. Because acute damage to tissues can lead to inflammation and cell death (which, if not adequately repaired, results in chronic inflammation and fibrosis), the ongoing damage and insufficient repair mechanisms can cause a progressive decline in tissue function, ultimately leading to long-term complications such as fibrosis, organ dysfunction, or secondary malignancies. However, neither the target cell hypothesis nor the loss of parenchymal and vascular cells directly account for the fibrosis observed in organs such as the heart, lungs, kidney, and liver after radiation exposure. Interestingly, parallels can be drawn between radiation-induced fibrosis and wound healing: both involve the induction of cytokine cascades, including tumour necrosis factor, interleukin-1, interleukin-6, and other growth factors, and the release of chemokines that recruit inflammatory cells. One key cytokine implicated in radiotherapy-related toxicity is transforming growth factor-β (TGF-β), which plays a crucial role in various pathological conditions,[55] including radiation-induced fibrosis.[56] Radiation exposure can trigger the cellular release of TGF-β and its dissociation from latency associated peptide, which normally maintains TGF-β in an inactive state. Activated TGF-β promotes the recruitment, proliferation, and activation of fibroblasts, leading to secretion of collagen into the extracellular matrix.

The wound healing response is often self-limiting, but in the case of pathological fibrosis in the post-radiation setting, the process could be perpetuated over the course of years by activation of feed-forward loops that trigger further inflammation and fibrosis (figure 2). Proposed reasons for this activation include the generation of hypoxia in irradiated tissues due to endothelial cell loss[57] and a disruption in the homoeostatic control of reactive oxygen species and reactive nitrogen species, which can also lead to TGF-β activation.[54] In radiation-induced fibrosis, particularly in the kidneys and possibly the lungs, the renin-angiotensis system has been implicated,[58] in addition to the senescence of healthy stem cells as a result of oxidative stress and DNA damage. This process results in an inability to repopulate after the original cell deaths and in the advent of a senescence-associated secretory phenotype, which is characterised by

the presence of a complex mixture of mitogenic and immunomodulatory cytokines, accounting for the chronic and progressive nature of injury.

Animal data have suggested that radiation-induced apoptosis could be responsible for many of the late effects observed in humans, but a causative association in humans has been difficult to establish. Ultimately, the pathophysiology of radiation late effects is likely multifactorial, tissue-dependent or organ-dependent, and needs to be further investigated and understood so that approaches to mitigate the risk of toxic effects can be developed.

Optimisation of selection of patients for radiotherapy

As for any other cancer treatment option, the decision to offer and recommend radiotherapy can only be made after a thorough patient evaluation and discussion of the potential benefits and risks associated with therapy. In this section, we will review specific situations in which the use of radiotherapy might be contraindicated (such as with specific genetic syndromes and medical conditions) and propose best practices for selection of patients to receive radiotherapy.

Certain genetic disorders can predispose patients to an excessive risk of complications from radiotherapy. Although rare, conditions such as ataxia–telangiectasia, Fanconi anaemia, and Nijmegen breakage syndrome share a common pathophysiology of defective DNA damage repair and can cause hypersensitivity to radiotherapy of a factor of two to four times that of the general population.[59] Collagen vascular diseases are a heterogeneous classification of systemic autoimmune connective tissue disorders and include rheumatoid arthritis, systemic lupus erythematosus, and scleroderma. They share a similar pathophysiology marked by vascular inflammation, obliteration, and fibrosis, with systemic and visceral effects. Therefore, the risk of radiotherapy to augment adverse events in these tissues has led to consideration of a concomitant diagnosis of collagen vascular disease to potentially be a relative contraindication to radiotherapy. The evidence and literature supporting such a practice, however, is variable. Reviews of studies have documented higher occurrences of acute and late toxic effects in patients with systemic autoimmune connective tissue disorders,[60] whereas others have reported negligible (<2%) rates of grade 4 or 5 toxic effects,[61] and no difference between patients with collagen vascular diseases and controls.[62] These data are challenging to interpret and apply to clinical practice because of variables such as the heterogeneity in collagen vascular diseases subtype and severity, details of radiotherapy (dose, anatomic site, and volume of radiation), and concurrent medical therapies (medications for collagen vascular diseases and chemotherapy), all of which can affect the risk of toxic effects. For example, patients with specific autoimmune connective tissue disorders, such as scleroderma or systemic lupus erythematosus might be at high risk of developing complications,[60,62–64] particularly with pelvic radiation.[62] The decision of whether to offer radiotherapy, therefore, needs to consider these variables and factors on an individual, patient-specific basis.

In order to assess how these variables affect the therapeutic ratio for patients who might be particularly sensitive to radiotherapy, best practices to mitigate the risk of toxic effects, and factors for clinicians to consider when evaluating a patient for radiotherapy are summarised in panel 1.

Management of toxic effects without treatment cessation

Radiotherapy can cause clinically significant acute side-effects, which can lead to treatment delay or cessation. In this section, we review specific situations for which radiotherapy cannot or should not be interrupted, discuss the importance of symptom management and supportive care to minimise treatment breaks, and outline best clinical practices to either avoid or minimise treatment interruptions due to radiotherapy-induced toxic effects.

From initiation to completion of treatment, a course of radiotherapy can be challenging from a medico-social perspective. Patients often require between five and ten radiation treatments per week, for up to 7 weeks. During this time, due to the multidisciplinary nature of cancer care, the incorporation of other treatments (such as surgery or chemotherapy) add to the burden of treatment—not only medical (ie, due to toxicity), but also financial, logistical, and social. Treatment delays and interruptions, therefore, are not uncommon. Even in well resourced environments such as academic, comprehensive cancer centres,[72] or as part of randomised clinical trials,[73] treatment can be suboptimal, with as many as 20–25% of all patients missing radiotherapy sessions and deviating from the originally intended time course. These delays highlight the scope and severity of the challenges that patients face when undergoing cancer therapy. Treatment interruptions are deleterious. Even when missed treatments are ultimately rescheduled and accounted for, midcourse interruptions and delays in radiotherapy can allow for accelerated tumour cell repopulation, which may result in poor disease outcomes such as compromised locoregional control and reduced recurrence-free and overall survival.[72] Patients with specific cancers, such as head and neck tumours[74] or cervical cancer,[75] for whom treatment prolongation has been associated with a decrease in local control and overall survival of 1% per day of missed treatment, could be at particularly high risk of worse outcomes from treatment interruptions.

Proactive and reactive strategies to avoid or make up for treatment interruptions are of crucial importance for these patients. Such strategies are multidisciplinary in

***Panel 1*: Factors to consider when evaluating a patient for radiotherapy**

Are viable alternatives to radiotherapy available?

Can other treatment options (eg, surgery) provide similar disease outcomes as those attainable with radiotherapy? Examples include surgical resection or active surveillance for patients with low-risk prostate cancer, or surgery alone for appropriately selected patients with low-risk breast cancer, who might have such a small absolute benefit in the reduction of local recurrence with the addition of radiotherapy that avoidance of radiotherapy might be a reasonable option. If so, and if an alternative treatment would eliminate the need for radiotherapy, the alternative should be discussed and considered. When several potential treatment options are under consideration, evaluation in a multidisciplinary clinic setting (whereby an expert in each therapeutic approach sees and assesses the patient before multidisciplinary discussion) is recommended. Patients should be actively involved in the subsequent conversations and in the decision-making process with their care providers (shared decision making). Patients engaged in shared decisions more often report satisfaction with their physicians' communication and better quality of care.[65]

If radiotherapy is necessary, what can be done before or during treatment to minimise its toxicity?

Before treatment

Priority should be given to reducing the severity of comorbid conditions. Such prioritisation means that the treating radiation oncologist needs to communicate and work closely in collaboration with the physicians who treat, for example, a patient's concomitant diagnosis of a collagen vascular disease. Although the severity of collagen vascular diseases at the time of radiotherapy might influence a patient's risk of radiotherapy-induced toxic effects,[66,67] this risk is counterbalanced by the medications used to treat these conditions, which often act as radiosensitisers. For patients who would usually be recommended to receive chemotherapy in conjunction with radiotherapy, consultation and collaboration with a medical oncologist is paramount in the determination of the necessity for and role of chemotherapy for each specific patient. Additionally, modifications in the chemotherapy regimen or dosing can be considered on the basis of cancer type, treatment location, and toxic effect risk. The use of pharmacological agents for radioprotection, while appealing in concept, has mostly yielded no substantial improvements in outcome from clinical studies.[68] However, changes in radiation dose and fractionation could be of benefit. If a specific organ at risk is of particular concern, baseline organ function should be assessed before radiotherapy and integrated into the customisation of the radiotherapy plan. For example, if a patient with chronic graft-versus-host disease has lung disease, a ventilation–perfusion scan can be used to determine the areas of functional lung to avoid irradiating; however, ventilation–perfusion scans are not reconstructed in 3D space, so incorporation of its information into radiotherapy treatment planning is difficult. Similarly, a split renal function scan can help ascertain whether one kidney functions better than the other and should thus be selectively avoided. Finally, new functional data can emerge and become important as in the case of the effective dose to immune cells, which is now becoming an important predictor of injuries to the immune system by radiotherapy. Thus, assessing organ function before treatment can help to identify areas to be preferentially spared during irradiation to preserve organ function after treatment.

During treatment

Important factors to consider are dose of radiation (dose per fraction and total dose) and the healthy tissue and organs at risk of toxic effects. Although stereotactic body radiotherapy or hypofractionated radiotherapy of some sites (eg, breast) have been shown to be effective and well tolerated, caution is needed when irradiating large volumes of sensitive healthy tissues (eg, the brachial plexus and mucosal structures in the head and neck area), especially in combination with systemic therapies, given that hypofractionation can lead to increased toxicity in those cases.[69] In patients who are at particularly high risk (eg, due to collagen vascular disease subtype and radiotherapy site) or who have early and unusual signs of acute toxic effects, careful monitoring and symptom management is essential. Consistent and close monitoring and early implementation of aggressive symptom management can improve tolerance, reduce risk of toxic effects, and improve outcomes.[70,71] In particularly severe cases, modifications in the planned radiotherapy course, such as planned treatment breaks, reduction of daily radiation fraction size, volume, or total dose might need to be considered on a case-by-case basis and discussed and reviewed with the patient at time of consultation and during treatment.

nature, with approaches focusing on both medical and social barriers to compliance. Medical interventions range from better preventive care, such as symptom and pain management, to technological advances in radiotherapy delivery. Consistent and careful evaluations for symptom management can reduce treatment deviations, decrease rates of hospitalisation, and improve outcomes.[70] Early implementation of symptom-focused care in conjunction with standard-of-care therapy not only improves quality of life but also survival.[71]

Technological advances in radiotherapy delivery techniques and technologies can also play a part in mitigating treatment interruptions. Conformal radiotherapy, such as intensity-modulated radiotherapy, which better spares healthy tissues and organs, has been shown to substantially decrease toxicity and improve patient quality of life.[2] Advances in radiation dosing and delivery, such as with hypofractionation and stereotactic body radiotherapy, have helped to minimise the logistical, social, and financial burden to a patient,

for whom a course of radiotherapy becomes feasible in a shorter number of treatments over a span of 1–3 weeks. Equally important are ancillary services, which range from patient navigation,[76] assistance with transportation,[77] and management of comorbid conditions such as mood disorders.[78] Use of a multifaceted and multidisciplinary, holistic, patient-centred approach to address all possible barriers to treatment tolerance and compliance will allow optimal management of radiation-induced toxic effects and ensure the best possible outcomes (panel 2).

Monitoring of late toxic effects in long-term radiotherapy survivors

In some patients, radiotherapy can cause late morbidity that is sometimes not observed for months, years, or even decades after completion of radiotherapy, and which greatly impair quality of life for long-term cancer survivors. In this section, we review and summarise current efforts for monitoring late effects and propose best practices for practising oncologists and primary care providers to monitor and ameliorate radiotherapy-induced late effects.

Many late toxic effects differ from acute toxic effects in signs, symptoms, and healthy tissue affected. Therefore, to best monitor for, and manage, late toxic effects, patients should be followed up regularly and consistently after treatment completion. The Institute of Medicine, in its report *From Cancer Patient to Cancer Survivor: Lost in Transition*[79] specifies four key aspects of survivorship care: first, prevention of recurrent and new cancers and of other late effects; second, surveillance for cancer spread, recurrence, second cancers, and medical and psychosocial late effects; third, intervention for consequences of cancer and its treatment (eg, medical problems, symptoms, psychological distress of cancer survivors and their caregivers, and concerns related to employment, insurance, and disability); and fourth,

***Panel 2*: Measures to minimise the burden of radiotherapy toxic effects**

Before treatment

- Assessment of potential social or logistical challenges: clinicians should facilitate a meeting between the patient and a navigator or social worker who can assess needs such as transportation, lodging, and leave of absence from work. Assistance can be provided by means of provision of reliable daily transportation, convenient long-term lodging, and completion of required paperwork for medical leave.
- Management of comorbidities: clinicians should communicate with a patient's other providers to ensure that all potential comorbid conditions are being optimally managed throughout treatment so as to not adversely affect the patient.
- Ancillary services: other services should be consulted depending on the specific needs of a patient or the planned treatment. Examples include smoking cessation (for patients receiving treatment for lung cancer or head and neck cancer), alcohol cessation (head and neck cancer), nutritional support or feeding tube placement (for patients entering treatment in a malnourished state), and fertility services (for patients who desire to have children and will receive fertility-affecting treatments, such as pelvic radiotherapy or chemotherapy).
- Symptom management and optimisation: symptom management should be assessed and implemented before treatment initiation, with an optimised regimen in place to promote patient comfort and compliance before, during, and after treatment.

During treatment

- Regular (at least weekly) visits with the treating radiation oncology team: regular assessment by the treating radiation oncologist (or an advanced practice provider, such as a physician's assistant or a nurse practitioner) to assess symptoms (as related to disease or treatment) and continuation or modification of symptom management as clinically indicated throughout the course of treatment. Patient needs should be assessed on the basis of physical, social, logistical, or financial burdens, with corresponding referrals to appropriate services (social work and counselling).
- Treatment adaptation: disease response and patient tolerance and compliance should be monitored during the course of treatment. Interventions such as adaptation of the radiotherapy plan on the basis of anatomic change from disease response, or modification of the dose, scheduling, and fractionation of radiotherapy as clinically indicated based on patient tolerance can be implemented as needed.
- Communication: regular communication between the treating radiation oncologist and medical oncologist is recommended throughout the treatment course to facilitate decisions on the radiotherapy or chemotherapy regimen on the basis of patient-specific factors, such as tolerance and sensitivity to toxicity. Towards the latter stages of a course of chemoradiation, radiation oncologists and medical oncologists should discuss the appropriateness of continuing radiotherapy even when further systemic therapy cannot be safely given.

After treatment

- Regular inspection visits: providers should see patients at a regular interval following completion of radiotherapy to assess late toxic effects and recovery progress. Interventions and medications should be adjusted as clinically indicated on the basis of persistence or resolution of symptoms secondary to disease or treatment.
- Survivorship and support groups: patients and their caregivers should be offered and connected to cancer survivorship and support groups. These groups provide resources and support to patients and families at various points during a patient's treatment for cancer.

coordination between specialists and primary care providers to ensure that all of the survivor's health needs are met.

The report recommended that a survivorship care plan, comprising a summary of the patient's cancer diagnosis, treatment summary, and follow-up care plan, be developed for each patient to communicate and coordinate survivorship care. The barriers to such an undertaking are multiple, including the additional time required by the primary oncologic provider, inexperience in survivorship care, and little coordination in sharing survivorship with other involved care providers. Although a majority of radiation oncologists discuss plans for future care with their patients, few provide a written survivorship care plan to their patients or their primary care physicians,[80] despite evidence that patients are more likely to receive recommended care when follow-up is shared by their oncologists and primary care physician.[81] Radiation oncologists should therefore maintain communication with a patient's primary care physician from the time of diagnosis and throughout treatment and post-treatment care, sharing follow-up and survivorship.

In follow-up care, attention to specific symptoms (based on cancer type and treatment) by the provider and via patient-reported outcomes is recommended. Two common toxic effects reporting scales used by providers are the Radiation Therapy Oncology Group[6] and the Common Terminology Criteria for Adverse Events. Radiation toxicity reporting transitioned from the Radiation Therapy Oncology Group toxicity scale to the Common Terminology Criteria for Adverse Events with the release of Common Terminology Criteria for Adverse Events version 2.0 in 1999.[7] However, patient-reported outcomes are also important and should not be neglected, because providers' and patients' perspectives on toxicity might differ[82,83] and because patient-reported outcomes provide valuable direct insight on the long-term negative effect that treatment-related toxic effects has on patients.[84] To assist with this effort, The National Cancer Institute Clinical Trials Planning Meeting was convened in 2011 to help establish a standard set of patient-reported outcomes domains to be routinely collected in clinical trials.[85,86] These recommendations are customisable, for example for patients with ovarian,[87] head and neck,[88] and prostate cancer.[89]

For more on **Common Terminology Criteria for Adverse Events** see https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

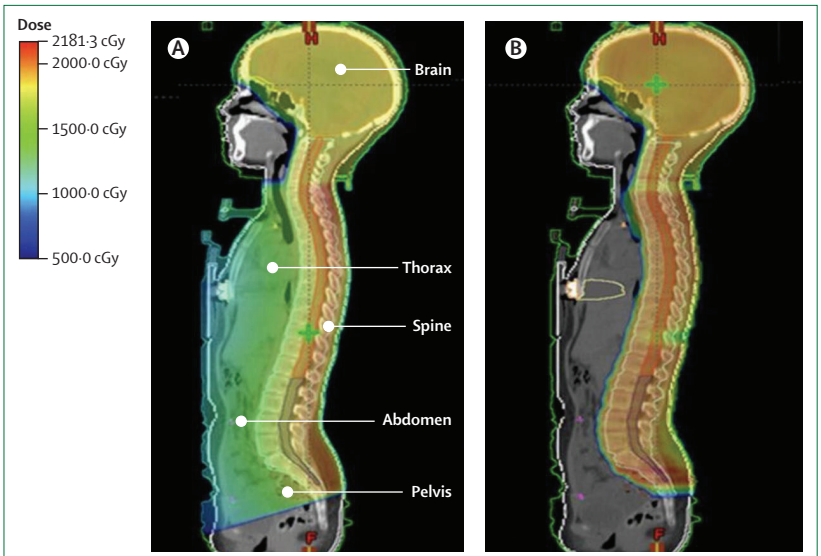

Figure 3: **Craniospinal irradiation plans for a prepubertal paediatric patient**
Patient with a paediatric brain tumour, for whom radiotherapy to the brain and spinal column was required at a dose of 2000 cGy, with (A) a typical photon-based radiotherapy plan compared to a (B) proton plan. The patient received proton therapy, with no dose to critical healthy tissues and organs in the thorax, abdomen, and pelvis (compared with 1500 cGy incidental dose that would have been delivered with photon-based radiotherapy).

Novel technologies for toxicity mitigation

Various radiotherapy techniques and technologies could be chosen to deliver the intended dose to the target and minimise the dose to the organs at risk, with particular consideration given to functional changes rather than relying solely on anatomical volume. The main risk prevention strategy for organs at risk is to minimise the radiation dose and exposed volume (integral dose). Tumour location is also a major determinant of toxic effect risk. Clinics should have available various radiotherapy technologies and equipment to best address patient-specific scenarios. The need for craniospinal irradiation in paediatric patients is perhaps the clearest example of such challenges faced clinically. The craniospinal axis is a very large target volume, which should be treated with relative homogeneity in children with medulloblastoma and other brain tumours. The target is geometrically close to many organs at risk, including the heart, lungs, breasts, bowel, pancreas, and ovaries. In addition, most patients who require craniospinal irradiation are young; as such, their tissues are particularly vulnerable to radiotherapy damage, and young patients might have many years of life in which to face late toxic effects. When 3D conformal radiotherapy is used to deliver craniospinal irradiation, the visceral organs at risk are exposed to unintentional radiotherapy; proton therapy allows elimination of this dose and reduces the expected resultant toxic effects (figure 3).[90,91] In the concurrent delivery of radiotherapy and chemotherapy, which is the standard-of-care curative treatment for various types of cancer, the selection of the radiotherapy technique can potentially affect clinical outcomes. While results of completed phase 3 randomised trials comparing proton versus photon therapy for intensity-modulated proton therapy are awaited (eg, NCT01993810), proton therapy could prove to be most useful in situations where dose–volume metrics for organs at risk are exceeded in intensity-modulated radiotherapy plans. This benefit is suggested by a retrospective, non-randomised comparative effectiveness study, which showed that the use of proton therapy concurrently with chemotherapy was linked to

statistically significant fewer acute adverse events, with similar disease-free and overall survival as compared with concurrent photon therapy.[92] Additionally, a randomised phase 2b trial for locally advanced oesophageal cancer showed a reduced risk and severity of toxic effects with proton therapy compared with intensity-modulated radiotherapy, while maintaining similar progression-free survival.[93] The use of image-guided radiotherapy with onboard imaging (either CT or MRI) improves accuracy by reducing day-to-day variation and allowing for reduction in planning target volume margins. The use of daily image-guided radiotherapy to make image-based adaptations on the radiotherapy plan is the basis of adaptive radiotherapy (adapting the radiotherapy plan throughout the course of treatment to ensure maximum conformality of radiotherapy dose to tumour while minimising dose to healthy organs), which has been prospectively shown to clinically reduce radiotherapy toxic effects[94] by reducing unintended irradiation of healthy tissues. For mobile tumours, such as those close to the diaphragm, tumour motion mitigation is another technological challenge. Examples of tumours often benefiting from motion management techniques include lower lobe lung and liver cancers. The entire path of the tumour can be treated during ventilatory motion (defined using four-dimensional CT); alternatively, tumour motion (eg, by abdominal compression or deep inspiration breath–hold) can be decreased to reduce the amount of healthy tissue in the treatment volume. Gating mechanisms use either surface anatomy (eg, camera-based systems) or internal anatomy (eg, implanted fiducial markers, transponders, or MRI-based onboard imaging) to turn the beam off and on when the visualised tumour (or surrogate marker) is within the treatment volume. For patients receiving radiotherapy for prostate cancer, metallic fiducials can be placed in the prostate gland to aid in visualisation for daily image guidance, and a gel spacer can be placed between the anterior rectal wall and the prostate gland. Fiducials allow more certainty in daily set up and a reduction in planning target volume margins, whereas the gel space increases the distance between the radiated target (prostate) and a nearby healthy organ (rectal), thereby reducing the risk of off-site toxic effects.

The future of radiotherapy

In recent years, the field of radiotherapy has witnessed substantial technological innovation, leading to a new era of precision and efficacy in cancer treatment. In this section, we aim to explore cutting-edge advancements and innovative approaches to improving conformity and accuracy, minimising side-effects, and increasing cost effectiveness.

The advent of ultra-high dose rate, also known as FLASH radiotherapy, was an important advance in radiotherapy delivery. FLASH radiotherapy is characterised by the administration of doses of radiotherapy at an unprecedented rate, typically exceeding 40 Gy/s. Unlike conventional radiotherapy, which administers radiation over several minutes (0·01–0·03 Gy/s), FLASH radiotherapy delivers the same dose within a fraction of a second. This rapid delivery of the same total dose has been shown in preclinical models to improve the therapeutic index of radiotherapy by decreasing healthy tissue damage while maintaining tumour response compared with standard radiotherapy.[95,96] Several preclinical studies have shown significant sparing of healthy tissues with FLASH radiotherapy, particularly in organs at risk such as the brain, heart, head and neck, skin, and intestine, leading to reduced acute and late toxic effects.[97–100] The first-in-human randomised trial of FLASH proton radiotherapy, focusing on patients with non-spine bone metastases, established the feasibility of this technique and showed that treatment efficacy and safety profiles were similar to those seen with conventional dose rate photon radiotherapy.[101] Future insights into the treatment effectiveness and toxicity profiles of FLASH radiotherapy are expected from several clinical trials, such as the ongoing phase 2 trial with patients with localised cutaneous squamous cell carcinoma or basal cell carcinoma at the Centre Hospitalier Universitaire Vaudois (Lausanne, Switzerland; NCT05724875). These findings provide support for further exploration of FLASH radiotherapy in the treatment of patients with cancer. However, challenges remain, including the optimisation of treatment planning and delivery systems to ensure safe and effective implementation in clinical settings. Concurrently, the pluridirectional high-energy agile scanning electronic radiotherapy (PHASER)[102] has emerged as another potential innovative approach to radiotherapy that can produce very high-energy electrons (100–200 MeV). Unlike conventional linear accelerators, PHASER encompasses several fundamental innovations aimed at achieving nearly instantaneous delivery of highly precise image-guided radiotherapy. This approach aims to provide superior dose conformity, reduce the effects of tumour motion, and potentially leverage an enhanced FLASH radiobiological therapeutic index.

The combination of stereotactic body radiotherapy and immunotherapy has been hypothesised to improve survival by means of what is called the abscopal effect (whereby irradiation of a tumour site induces an increased immune response in unirradiated tumours elsewhere in the body). However, the abscopal effect is rarely observed in clinical practice, and robust evidence that the combination of radiotherapy and immunotherapy increases the probability of this effect is yet to observed. Multiple studies have yielded negative results,[103–105] which should temper enthusiasm for this approach. Nevertheless, stereotactic body radiotherapy can still provide durable control of oligometastatic or oligoprogressive deposits in patients receiving systemic

therapy and might delay progression and enhance survival. Ongoing clinical investigations are needed to clarify the potential benefits and limitations of combining radiotherapy with systemic treatments.

Temporal and spatial fractionation in radiotherapy are innovative strategies designed to improve the therapeutic ratio by optimising the distribution of radiation doses across time and space. In temporal fractionation, the timing and schedule of radiation doses are adjusted to exploit the differential repair capacities of healthy and tumour tissues, potentially enabling higher doses to tumours while sparing healthy tissue. Spatially fractionated radiotherapy delivers non-uniform radiation doses to the tumour by creating alternating high-dose and low-dose regions within the target area, which is especially beneficial for heterogeneous tumour microenvironments with severe hypoxic areas requiring higher, ablative radiation doses.[106] An example is 3D lattice radiotherapy, which delivers a spatially fractionated radiotherapy in 3D, essentially creating a network of high-dose vertices within the tumour while minimising radiation exposure to surrounding healthy tissue.[107] One retrospective study showed that stereotactic body radiotherapy for partial tumour irradiation, targeting hypoxic segments of unresectable bulky tumours, effectively induced local bystander effects without causing acute or late toxic effects of any grade.[108] Working groups in NRG Oncology and in the American Association of Physicists in Medicine recommended improving spatially fractionated radiotherapy in cancer treatment by developing clinical guidelines, enhancing treatment planning systems, standardising reporting templates, and advancing radiobiological models through preclinical studies and clinical trials.[109]

Adaptive radiotherapy is an emerging approach in cancer treatment and is becoming more widely available in clinical practice. It uses real-time data and advanced imaging to adjust radiotherapy plans during the course of therapy. Adaptive radiotherapy can be applied to manage patient-specific treatment variations, such as systematic changes in weight, tumour and organ geometry, biological responses, and stochastic factors such as organ deformation and movements due to respiration and peristalsis. Adaptive radiotherapy has been reported to offer a dosimetric benefit of up to a 10 Gy reduction in the mean parotid gland dose compared with non-adaptive radiotherapy, and retrospective studies suggest potential clinical benefits, including improved quality of life and local disease control.[110–112] However, in a phase 3 randomised clinical trial, adaptive radiotherapy did not improve salivary flow, patient-reported outcome scores, or rates of toxic effects compared with standard intensity-modulated radiotherapy.[113] Several ongoing clinical trials (eg, NCT02031250, NCT03416153, NCT03224000, and NCT01504815) are investigating functional subvolume boosting and adjustments to dose schemes based on functional imaging. The integration of artificial intelligence (AI) and machine learning algorithms can make adaptive radiotherapy more efficient, enabling faster and more accurate adjustments based on patient data.

Modern radiotherapy approaches have enhanced precision and personalisation, but adaptation to tumour biology remains a challenge. Biomarkers to predict tumour and healthy tissue radiosensitivity (eg, gene signatures, protein concentrations, and radiogenomics) are needed to enable more personalised decision making, dosing, and treatment planning. Although proteins remain the most common cancer biomarkers, other molecules, such as circulating cell-free tumour DNA, have emerged as promising alternatives for the identification of cancer biomarkers. Liquid biopsy involves analysing cell-free DNA and other cellular components released by dying or damaged cells into the bloodstream, which carry the genetic and epigenetic features of the original tumour, including somatic mutations and DNA methylation.[114,115] To date, analysis of cell-free DNA has not been routinely used in radiotherapy dosing or scheduling. In virus-associated cancers such as Epstein–Barr virus-related nasopharyngeal and human papillomavirus-related oropharyngeal cancers, measuring circulating tumour-derived DNA or viral load during treatment has shown promise in guiding therapy intensification or deintensification.[116,117] Although promising, validation and further research are required before such approaches become routine standard of care in radiotherapy.

The integration of AI in radiotherapy offers great potential to enhance precision and personalisation in cancer treatment. AI-driven tools are being used to improve tumour contouring, dose optimisation, and treatment planning, reducing variability and increasing accuracy in radiation delivery.[118–120] By analysing large datasets from previous treatments, machine learning algorithms can predict optimal radiation doses and anticipate toxic effects, resulting in more efficient and effective therapies. Machine learning can also automate complex processes and enable real-time adjustments during treatment, leading to improved patient outcomes. Moreover, AI has substantially shortened treatment planning time, using knowledge-based planning and deep learning to produce plans equivalent to those produced manually by medical dosimetrists, physicists, and radiation oncologists.[121] Its role in prediction and prognosis, particularly through radiogenomics, continues to grow and advance. Despite ongoing legal, ethical, and regulatory challenges, such as data ownership, informed consent, and reproducibility, AI continues to have a growing effect and shows potential for future advancements in radiation oncology.

By capitalising on such groundbreaking advancements, clinicians can introduce a new era of personalised and precise radiotherapy, offering improved outcomes and quality of life for patients with cancer worldwide.

Radiotherapy has been an integral part of cancer treatment for over a century. Although it can induce long-term toxic effects in some patients, its ability to precisely target tumours while sparing healthy tissue, alongside ongoing advances into the mitigation of side-effects, means that radiotherapy will continue to be an effective and indispensable therapeutic approach in the years to come.

Contributors

IIV, DEC, AM, JDB, and AL drafted the manuscript. IIV, CEH-K, and AL prepared the figures. All authors contributed to the completion of the table and contributed to writing and revision of the Review.

Declaration of interests

This work received no dedicated funding. IIV reports research funding from the Institute for Translational Medicine and Therapeutics, American Cancer Society, the Thomas B and Jeannette E Laws McCabe Fund, and the University Research Foundation, paid to institution; honoraria from the University of Arkansas (Fayetteville, AR, USA); consulting fees from Mevion Medical Systems; and travel support from the Flash Radiotherapy & Particle Therapy (FRPT) and Radiation Research Society (RRS) to attend the FRPT and RRS meetings. DEC is an employee at the US National Institutes of Health; and is a non-fiduciary, unpaid, nominating committee member of the American Society of Radiation Oncology. BK reports research funding from the US National Institutes of Health, the American Heart Association, and the Pfizer Investigator Initiated Grant, paid to institution; consulting fees from Bristol Myers Squibb, AstraZeneca, Roche, and Pfizer; honoraria from Medscape, UpToDate, and the American College of Cardiology Cardio-Oncology CME Course; support to attend the American Society of Clinical Oncology and American Association for Cancer Research meetings; is Editor-in-Chief of *JACC CardioOncology*; and is part of the Board of Trustees of the American College of Cardiology. CK reports research funding from the US National Institutes of Health, The Mark Foundation for Cancer Research, and Ion Beam Applications group through a sponsored research agreement to his institution; honoraria from MD Anderson Cancer Center, Dartmouth University (Hanover, NH, USA), and Duke University (Durham, NC, USA); support from the American Association for Cancer Research to attend the American Association for Cancer Research meeting; and is a Scientific Founder and majority stock option holder of Veltion Therapeutics. AM reports honoraria from the Oncology Nursing Society and University of Washington (Washington, DC, USA). JDB reports honoraria from Mevion Medical Systems. AL reports research funding from the US National Institutes of Health and the Patient-Centered Outcomes Research Institute, honoraria from Galera Therapeutics for participating in their advisory board, and honoraria from Janssen Pharmaceuticals for participation in their steering committee. All other authors declare no competing interests.

Acknowledgments

IIV acknowledges support from IRG-22-150-41-IRG from the American Cancer Society. CK and AL acknowledge support from NIH 5P01CA257904-03.

References

1 Kaye GWC. Wilhelm Conrad Röntgen: and the early history of the roentgen rays. *Nature* 1934; **133:** 511–13.
2 Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011; **12:** 127–36.
3 Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer* 2005; **104:** 1129–37.
4 Bentzen SM, Constine LS, Deasy JO, et al. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010; **76** (suppl)**:** S3–9.
5 Grimm J, Marks LB, Jackson A, Kavanagh BD, Xue J, Yorke E. High dose per fraction, hypofractionated treatment effects in the clinic (HyTEC): an overview. *Int J Radiat Oncol Biol Phys* 2021; **110:** 1–10.
6 Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; **31:** 1341–46.
7 Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: version 2.0. An improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys* 2000; **47:** 13–47.
8 Eriguchi T, Takeda A, Sanuki N, et al. Acceptable toxicity after stereotactic body radiation therapy for liver tumors adjacent to the central biliary system. *Int J Radiat Oncol Biol Phys* 2013; **85:** 1006–11.
9 Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010; **76** (suppl)**:** S10–19.
10 Guha C, Kavanagh BD. Hepatic radiation toxicity: avoidance and amelioration. *Semin Radiat Oncol* 2011; **21:** 256–63.
11 Birgisson H, Påhlman L, Gunnarsson U, Glimelius B. Late adverse effects of radiation therapy for rectal cancer—a systematic overview. *Acta Oncol* 2007; **46:** 504–16.
12 Holm T, Singnomklao T, Rutqvist LE, Cedermark B. Adjuvant preoperative radiotherapy in patients with rectal carcinoma. Adverse effects during long term follow-up of two randomized trials. *Cancer* 1996; **78:** 968–76.
13 Broggi S, Passoni P, Tiberio P, et al. Stomach and duodenum dose-volume constraints for locally advanced pancreatic cancer patients treated in 15 fractions in combination with chemotherapy. *Front Oncol* 2023; **12:** 983984.
14 Brick IB. Effects of million volt irradiation on the gastrointestinal tract. *AMA Arch Intern Med* 1955; **96:** 26–31.
15 Holt GE, Griffin AM, Pintilie M, et al. Fractures following radiotherapy and limb-salvage surgery for lower extremity soft-tissue sarcomas. A comparison of high-dose and low-dose radiotherapy. *J Bone Joint Surg Am* 2005; **87:** 315–19.
16 Deng J, Ridner SH, Dietrich MS, et al. Prevalence of secondary lymphedema in patients with head and neck cancer. *J Pain Symptom Manage* 2012; **43:** 244–52.
17 Shaitelman SF, Chiang YJ, Griffin KD, et al. Radiation therapy targets and the risk of breast cancer-related lymphedema: a systematic review and network meta-analysis. *Breast Cancer Res Treat* 2017; **162:** 201–15.
18 Deng J, Wulff-Burchfield EM, Murphy BA. Late soft tissue complications of head and neck cancer therapy: lymphedema and fibrosis. *J Natl Cancer Inst Monogr* 2019; **2019:** lgz005.
19 Overgaard M, Bentzen SM, Christensen JJ, Madsen EH. The value of the NSD formula in equation of acute and late radiation complications in normal tissue following 2 and 5 fractions per week in breast cancer patients treated with postmastectomy irradiation. *Radiother Oncol* 1987; **9:** 1–11.
20 Lee TF, Yeh SA, Chao PJ, et al. Normal tissue complication probability modeling for cochlea constraints to avoid causing tinnitus after head-and-neck intensity-modulated radiation therapy. *Radiat Oncol* 2015; **10:** 194.
21 Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991; **21:** 109–22.
22 Sabino L, Marino S, Falsaperla R, Pisani F, Massimino C, Pavone P. Celiac disease and headache in children: a narrative state of the art. *Acta Biomed* 2020; **91:** e2020056.
23 Pekic S, Miljic D, Popovic V. Hypopituitarism following cranial radiotherapy. In: Feingold KR, Anawalt B, Blackman MR, et al, eds. Endotext. MDText.com, Inc, 2000.
24 Delanian S, Lefaix JL, Pradat PF. Radiation-induced neuropathy in cancer survivors. *Radiother Oncol* 2012; **105:** 273–82.
25 National Comprehensive Cancer Network. NCCN guidelines for non-small cell lung cancer, version 7. 2024. 2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed Oct 1, 2024).
26 Mitchell JD, Cehic DA, Morgia M, et al. Cardiovascular manifestations from therapeutic radiation: a multidisciplinary expert consensus statement from the International Cardio-Oncology Society. *JACC Cardiooncol* 2021; **3:** 360–80.
27 Parsons JT, Bova FJ, Fitzgerald CR, Mendenhall WM, Million RR. Severe dry-eye syndrome following external beam irradiation. *Int J Radiat Oncol Biol Phys* 1994; **30:** 775–80.

28 Treister NS, Brennan MT, Sollecito TP, et al. Exposed bone in patients with head and neck cancer treated with radiation therapy: an analysis of the observational study of dental outcomes in head and neck cancer patients (OraRad). *Cancer* 2022; **128:** 487–96.

29 Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet* 2019; **393:** 40–50.

30 Rooney MK, Andring LM, Corrigan KL, et al. Hypothyroidism following radiotherapy for head and neck cancer: a systematic review of the literature and opportunities to improve the therapeutic ratio. *Cancers* 2023; **15:** 4321.

31 Ling S, Bhatt AD, Brown NV, et al. Correlative study of dose to thyroid and incidence of subsequent dysfunction after head and neck radiation. *Head Neck* 2017; **39:** 548–54.

32 Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016; **17:** 1047–60.

33 Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet* 2019; **394:** 385–95.

34 Morris L, Do V, Chard J, Brand AH. Radiation-induced vaginal stenosis: current perspectives. *Int J Womens Health* 2017; **9:** 273–79.

35 Bradley JD, Hu C, Komaki RR, et al. Long-term results of NRG Oncology RTOG 0617: standard- versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 2020; **38:** 706–14.

36 Coia LR, Myerson RJ, Tepper JE. Late effects of radiation therapy on the gastrointestinal tract. *Int J Radiat Oncol Biol Phys* 1995; **31:** 1213–36.

37 Algammal AM, Eidaroos NH, Alfifi KJ, et al. *opr*L gene sequencing, resistance patterns, virulence genes, quorum sensing and antibiotic resistance genes of XDR *Pseudomonas aeruginosa* isolated from broiler chickens. *Infect Drug Resist* 2023; **16:** 853–67.

38 Yegya-Raman N, Wang K, Kim S, et al. Dosimetric predictors of symptomatic cardiac events after conventional-dose chemoradiation therapy for inoperable NSCLC. *J Thorac Oncol* 2018; **13:** 1508–18.

39 Atkins KM, Chaunzwa TL, Lamba N, et al. Association of left anterior descending coronary artery radiation dose with major adverse cardiac events and mortality in patients with non-small cell lung cancer. *JAMA Oncol* 2021; **7:** 206–19.

40 Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015; **16:** 187–99.

41 Rosen II, Fischer TA, Antolak JA, et al. Correlation between lung fibrosis and radiation therapy dose after concurrent radiation therapy and chemotherapy for limited small cell lung cancer. *Radiology* 2001; **221:** 614–22.

42 Li W, Xiao H, Xu X, Zhang Y. The impact of radiotherapy on the incidence of secondary malignancies: a pan-cancer study in the US SEER cancer registries. *Curr Oncol* 2021; **28:** 301–16.

43 Gold DG, Neglia JP, Dusenbery KE. Second neoplasms after megavoltage radiation for pediatric tumors. *Cancer* 2003; **97:** 2588–96.

44 Burt LM, Ying J, Poppe MM, Suneja G, Gaffney DK. Risk of secondary malignancies after radiation therapy for breast cancer: comprehensive results. *Breast* 2017; **35:** 122–29.

45 Bagshaw HP, Arnow KD, Trickey AW, Leppert JT, Wren SM, Morris AM. Assessment of second primary cancer risk among men receiving primary radiotherapy *vs* surgery for the treatment of prostate cancer. *JAMA Netw Open* 2022; **5:** e2223025.

46 Wang W, Cui B, Nie Y, Sun L, Zhang F. Radiation injury and gut microbiota-based treatment. *Protein Cell* 2024; **15:** 83–97.

47 Reis Ferreira M, Pasto A, Ng T, et al. The microbiota and radiotherapy for head and neck cancer: what should clinical oncologists know? *Cancer Treat Rev* 2022; **109:** 102442.

48 Ellsworth SG. Field size effects on the risk and severity of treatment-induced lymphopenia in patients undergoing radiation therapy for solid tumors. *Adv Radiat Oncol* 2018; **3:** 512–19.

49 Jin JY, Hu C, Xiao Y, et al. Higher radiation dose to the immune cells correlates with worse tumor control and overall survival in patients with stage III NSCLC: a secondary analysis of RTOG0617. *Cancers* 2021; **13:** 6193.

50 Yu Y, Fu P, Jin JY, et al. Impact of effective dose to immune cells (EDIC) on lymphocyte nadir and survival in limited-stage SCLC. *Radiother Oncol* 2021; **162:** 26–33.

51 Xu C, Jin JY, Zhang M, et al. The impact of the effective dose to immune cells on lymphopenia and survival of esophageal cancer after chemoradiotherapy. *Radiother Oncol* 2020; **146:** 180–86.

52 Stewart FA, Akleyev AV, Hauer-Jensen JH, et al. ICRP publication 118: ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs-threshold doses for tissue reactions in a radiation protection context. *Ann ICRP* 2012; **41:** 1–322.

53 Hall EJ, Giaccia AJ. Radiobiology for the radiologist, 8th edn. Wolters Kluwer Health, 2018.

54 Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. *Nat Rev Cancer* 2006; **6:** 702–13.

55 Massagué J, Sheppard D. TGF-β signaling in health and disease. *Cell* 2023; **186:** 4007–37.

56 Martin M, Lefaix J, Delanian S. TGF-beta1 and radiation fibrosis: a master switch and a specific therapeutic target? *Int J Radiat Oncol Biol Phys* 2000; **47:** 277–90.

57 Vujaskovic Z, Anscher MS, Feng QF, et al. Radiation-induced hypoxia may perpetuate late normal tissue injury. *Int J Radiat Oncol Biol Phys* 2001; **50:** 851–55.

58 Robbins ME, Diz DI. Pathogenic role of the renin-angiotensin system in modulating radiation-induced late effects. *Int J Radiat Oncol Biol Phys* 2006; **64:** 6–12.

59 Alapetite C, Cosset JM, Bourguignon MH, Masse R. Genetic susceptibility to radiations. Which impact on medical practice? *Q J Nucl Med* 2000; **44:** 347–54.

60 Chon BH, Loeffler JS. The effect of nonmalignant systemic disease on tolerance to radiation therapy. *Oncologist* 2002; **7:** 136–43.

61 Lin D, Lehrer EJ, Rosenberg J, Trifiletti DM, Zaorsky NG. Toxicity after radiotherapy in patients with historically accepted contraindications to treatment (CONTRAD): an international systematic review and meta-analysis. *Radiother Oncol* 2019; **135:** 147–52.

62 Lin A, Abu-Isa E, Griffith KA, Ben-Josef E. Toxicity of radiotherapy in patients with collagen vascular disease. *Cancer* 2008; **113:** 648–53.

63 Morris MM, Powell SN. Irradiation in the setting of collagen vascular disease: acute and late complications. *J Clin Oncol* 1997; **15:** 2728–35.

64 Pinn ME, Gold DG, Petersen IA, Osborn TG, Brown PD, Miller RC. Systemic lupus erythematosus, radiotherapy, and the risk of acute and chronic toxicity: the Mayo Clinic Experience. *Int J Radiat Oncol Biol Phys* 2008; **71:** 498–506.

65 Kehl KL, Landrum MB, Arora NK, et al. Association of actual and preferred decision roles with patient-reported quality of care: shared decision making in cancer care. *JAMA Oncol* 2015; **1:** 50–58.

66 Robertson JM, Clarke DH, Pevzner MM, Matter RC. Breast conservation therapy. Severe breast fibrosis after radiation therapy in patients with collagen vascular disease. *Cancer* 1991; **68:** 502–08.

67 Delanian S, Maulard-Durdux C, Lefaix JL, Housset M. Major interactions between radiation therapy and systemic sclerosis: is there an optimal treatment? *Eur J Cancer* 1996; **32A:** 738–39.

68 Buentzel J, Micke O, Adamietz IA, Monnier A, Glatzel M, de Vries A. Intravenous amifostine during chemoradiotherapy for head-and-neck cancer: a randomized placebo-controlled phase III study. *Int J Radiat Oncol Biol Phys* 2006; **64:** 684–91.

69 Beitler JJ, Zhang Q, Fu KK, et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. *Int J Radiat Oncol Biol Phys* 2014; **89:** 13–20.

70 Mason H, DeRubeis MB, Foster JC, Taylor JM, Worden FP. Outcomes evaluation of a weekly nurse practitioner-managed symptom management clinic for patients with head and neck cancer treated with chemoradiotherapy. *Oncol Nurs Forum* 2013; **40:** 581–86.

71 Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363:** 733–42.

72 Ohri N, Rapkin BD, Guha C, Kalnicki S, Garg M. Radiation therapy noncompliance and clinical outcomes in an urban academic cancer center. *Int J Radiat Oncol Biol Phys* 2016; **95:** 563–70.

73 Khalil AA, Bentzen SM, Bernier J, et al. Compliance to the prescribed dose and overall treatment time in five randomized clinical trials of altered fractionation in radiotherapy for head-and-neck carcinomas. *Int J Radiat Oncol Biol Phys* 2003; **55:** 568–75.

74 Bese NS, Hendry J, Jeremic B. Effects of prolongation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. *Int J Radiat Oncol Biol Phys* 2007; **68:** 654–61.

75 Petereit DG, Sarkaria JN, Chappell R, et al. The adverse effect of treatment prolongation in cervical carcinoma. *Int J Radiat Oncol Biol Phys* 1995; **32:** 1301–07.

76 Freund KM, Battaglia TA, Calhoun E, et al. Impact of patient navigation on timely cancer care: the Patient Navigation Research Program. *J Natl Cancer Inst* 2014; **106:** dju115.

77 Salloum RG, Smith TJ, Jensen GA, Lafata JE. Factors associated with adherence to chemotherapy guidelines in patients with non-small cell lung cancer. *Lung Cancer* 2012; **75:** 255–60.

78 DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000; **160:** 2101–07.

79 Hewitt ME, Greenfield S, Stovall E. From cancer patient to cancer survivor : lost in transition. National Academies Press, 2006.

80 Frick MA, Rosenthal SA, Vapiwala N, Monzon BT, Berman AT. The state of survivorship care in radiation oncology: results from a nationally distributed survey. *Cancer* 2018; **124:** 2653–60.

81 Snyder CF, Frick KD, Kantsiper ME, et al. Prevention, screening, and surveillance care for breast cancer survivors compared with controls: changes from 1998 to 2002. *J Clin Oncol* 2009; **27:** 1054–61.

82 Slevin ML, Plant H, Lynch D, Drinkwater J, Gregory WM. Who should measure quality of life, the doctor or the patient? *Br J Cancer* 1988; **57:** 109–12.

83 Sarna L, Swann S, Langer C, et al. Clinically meaningful differences in patient-reported outcomes with amifostine in combination with chemoradiation for locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. *Int J Radiat Oncol Biol Phys* 2008; **72:** 1378–84.

84 Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008; **26:** 3770–76.

85 Gotay C. Core symptom measures in cancer clinical trials. *J Natl Cancer Inst* 2014; **106:** dju173.

86 Reeve BB, Mitchell SA, Dueck AC, et al. Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *J Natl Cancer Inst* 2014; **106:** dju129.

87 Donovan KA, Donovan HS, Cella D, et al. Recommended patient-reported core set of symptoms and quality-of-life domains to measure in ovarian cancer treatment trials. *J Natl Cancer Inst* 2014; **106:** dju128.

88 Chera BS, Eisbruch A, Murphy BA, et al. Recommended patient-reported core set of symptoms to measure in head and neck cancer treatment trials. *J Natl Cancer Inst* 2014; **106:** dju127.

89 Chen RC, Chang P, Vetter RJ, et al. Recommended patient-reported core set of symptoms to measure in prostate cancer treatment trials. *J Natl Cancer Inst* 2014; **106:** dju132.

90 Liu KX, Ioakeim-Ioannidou M, Susko MS, et al. A multi-institutional comparative analysis of proton and photon therapy-induced hematologic toxicity in patients with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2021; **109:** 726–35.

91 Vázquez M, Bachmann N, Pica A, et al. Early outcome after craniospinal irradiation with pencil beam scanning proton therapy for children, adolescents and young adults with brain tumors. *Pediatr Blood Cancer* 2023; **70:** e30087.

92 Baumann BC, Mitra N, Harton JG, et al. Comparative effectiveness of proton *vs* photon therapy as part of concurrent chemoradiotherapy for locally advanced cancer. *JAMA Oncol* 2020; **6:** 237–46.

93 Lin SH, Hobbs BP, Verma V, et al. Randomized phase IIB trial of proton beam therapy versus intensity-modulated radiation therapy for locally advanced esophageal cancer. *J Clin Oncol* 2020; **38:** 1569–79.

94 Bruynzeel AME, Tetar SU, Oei SS, et al. A prospective single-arm phase 2 study of stereotactic magnetic resonance guided adaptive radiation therapy for prostate cancer: early toxicity results. *Int J Radiat Oncol Biol Phys* 2019; **105:** 1086–94.

95 Favaudon V, Caplier L, Monceau V, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Sci Transl Med* 2014; **6:** 245ra93.

96 Vozenin MC, Bourhis J, Durante M. Towards clinical translation of FLASH radiotherapy. *Nat Rev Clin Oncol* 2022; **19:** 791–803.

97 Diffenderfer ES, Verginadis II, Kim MM, et al. Design, implementation, and in vivo validation of a novel proton FLASH radiation therapy system. *Int J Radiat Oncol Biol Phys* 2020; **106:** 440–48.

98 Velalopoulou A, Karagounis IV, Cramer GM, et al. FLASH proton radiotherapy spares normal epithelial and mesenchymal tissues while preserving sarcoma response. *Cancer Res* 2021; **81:** 4808–21.

99 Kim K, Kim MM, Skoufos G, et al. FLASH proton radiation therapy mitigates inflammatory and fibrotic pathways and preserves cardiac function in a preclinical mouse model of radiation-induced heart disease. *Int J Radiat Oncol Biol Phys* 2024; **119:** 1234–47.

100 Chowdhury P, Velalopoulou A, Verginadis II, et al. Proton FLASH radiotherapy ameliorates radiation-induced salivary gland dysfunction and oral mucositis and increases survival in a mouse model of head and neck cancer. *Mol Cancer Ther* 2024; **23:** 877–89.

101 Mascia AE, Daugherty EC, Zhang Y, et al. Proton FLASH radiotherapy for the treatment of symptomatic bone metastases: the FAST-01 nonrandomized trial. *JAMA Oncol* 2023; **9:** 62–69.

102 Maxim PG, Tantawi SG, Loo BW Jr. PHASER: a platform for clinical translation of FLASH cancer radiotherapy. *Radiother Oncol* 2019; **139:** 28–33.

103 Machiels JP, Tao Y, Licitra L, et al. Pembrolizumab plus concurrent chemoradiotherapy versus placebo plus concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (KEYNOTE-412): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2024; **25:** 572–87.

104 Schoenfeld JD, Giobbie-Hurder A, Ranasinghe S, et al. Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non-small-cell lung cancer refractory to previous PD(L)-1 therapy: an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol* 2022; **23:** 279–91.

105 Spaas M, Sundahl N, Kruse V, et al. Checkpoint inhibitors in combination with stereotactic body radiotherapy in patients with advanced solid tumors: the CHEERS phase 2 randomized clinical trial. *JAMA Oncol* 2023; **9:** 1205–13.

106 Yan W, Khan MK, Wu X, et al. Spatially fractionated radiation therapy: history, present and the future. *Clin Transl Radiat Oncol* 2019; **20:** 30–38.

107 Wu X, Perez NC, Zheng Y, et al. The technical and clinical implementation of LATTICE radiation therapy (LRT). *Radiat Res* 2020; **194:** 737–46.

108 Tubin S, Popper HH, Brcic L. Novel stereotactic body radiation therapy (SBRT)-based partial tumor irradiation targeting hypoxic segment of bulky tumors (SBRT-PATHY): improvement of the radiotherapy outcome by exploiting the bystander and abscopal effects. *Radiat Oncol* 2019; **14:** 21.

109 Li H, Mayr NA, Griffin RJ, et al. Overview and recommendations for prospective multi-institutional spatially fractionated radiation therapy clinical trials. *Int J Radiat Oncol Biol Phys* 2024; **119:** 737–49.

110 Castelli J, Simon A, Louvel G, et al. Impact of head and neck cancer adaptive radiotherapy to spare the parotid glands and decrease the risk of xerostomia. *Radiat Oncol* 2015; **10:** 6.

111 Capelle L, Mackenzie M, Field C, Parliament M, Ghosh S, Scrimger R. Adaptive radiotherapy using helical tomotherapy for head and neck cancer in definitive and postoperative settings: initial results. *Clin Oncol (R Coll Radiol)* 2012; **24:** 208–15.

112 Schwartz DL, Garden AS, Thomas J, et al. Adaptive radiotherapy for head-and-neck cancer: initial clinical outcomes from a prospective trial. *Int J Radiat Oncol Biol Phys* 2012; **83:** 986–93.

113 Castelli J, Thariat J, Benezery K, et al. Weekly adaptive radiotherapy *vs* standard intensity-modulated radiotherapy for improving salivary function in patients with head and neck cancer: a phase 3 randomized clinical trial. *JAMA Oncol* 2023; **9:** 1056–64.

114 Baev V, Koppers-Lalic D, Costa-Silva B. Liquid biopsy: current status and future perspectives. *Cancers* 2023; **15:** 3205.

115 McLaren DB, Aitman TJ. Redefining precision radiotherapy through liquid biopsy. *Br J Cancer* 2023; **129:** 900–03.

116 Leung SF, Chan KC, Ma BB, et al. Plasma Epstein–Barr viral DNA load at midpoint of radiotherapy course predicts outcome in advanced-stage nasopharyngeal carcinoma. *Ann Oncol* 2014; **25:** 1204–08.

117 Chera BS, Kumar S, Beaty BT, et al. Rapid clearance profile of plasma circulating tumor HPV type 16 DNA during chemoradiotherapy correlates with disease control in HPV-associated oropharyngeal cancer. *Clin Cancer Res* 2019; **25:** 4682–90.

118 Huynh E, Hosny A, Guthier C, et al. Artificial intelligence in radiation oncology. *Nat Rev Clin Oncol* 2020; **17:** 771–81.

119 Almeida ND, Shekher R, Pepin A, et al. Artificial intelligence potential impact on resident physician education in radiation oncology. *Adv Radiat Oncol* 2024; **9:** 101505.

120 Kawamura M, Kamomae T, Yanagawa M, et al. Revolutionizing radiation therapy: the role of AI in clinical practice. *J Radiat Res* 2024; **65:** 1–9.

121 Kalsi S, French H, Chhaya S, et al. The evolving role of artificial intelligence in radiotherapy treatment planning–a literature review. *Clin Oncol (R Coll Radiol)* 2024; **36:** 596–605.