

# Contemporary radiotherapy: present and future

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Oncology care is increasingly a multidisciplinary endeavour, and radiation therapy continues to have a key role across the disease spectrum in nearly every cancer. However, the field of radiation oncology is still one of the most poorly understood of the cancer disciplines. In this Review, we attempt to summarise and contextualise developments within the field of radiation oncology for the non-radiation oncologist. We discuss advancements in treatment technologies and imaging, followed by an overview of the interplay with advancements in systemic therapy and surgical techniques. Finally, we review new frontiers in radiation oncology, including advances within the metastatic disease continuum, reirradiation, and emerging types of radiation therapy.

## Introduction

Although the beginnings of modern radiotherapy can be traced back to the discovery of the x-ray in the late 1800s, the field of radiation oncology has had multiple renaissances since its formal inception six decades ago.<sup>1,2</sup> As imaging and treatment delivery techniques have improved, the applications of radiation oncology have expanded. Approximately half<sup>3,4</sup> of patients are estimated to receive radiotherapy at some point after a diagnosis of cancer, with indications spanning curative treatment to symptom palliation.

Close collaboration across oncological fields is crucial to improve treatment and ensure the optimal application of radiotherapy. There have been multiple advances in radiotherapy. For this Review, we aimed to provide a useful and pragmatic overview for non-radiation oncologists, with an emphasis on how technological enhancements have led to smaller treatment volumes, shorter treatment times, better outcomes, and decreased toxicity. We have focused on data from randomised trials, consensus guidelines, and promising emerging research that have transformed the field. We also look at the potential effect of current technologies and how they might shape the field during the coming decades.

## New technology: evolving radiotherapy

Improvements in diagnostic imaging, treatment planning, and treatment delivery have enabled more accurate and precise treatment of diseased tissue and avoidance of healthy tissues. This has expanded the so-called therapeutic window, the dose range in which

tumours can be effectively treated and side-effects can be minimised.

The evolution of modern radiotherapy is shown in figure 1. Historically, radiotherapy was planned and delivered in two dimensions, with treatment fields based on bony anatomy. Treatment fields were large and the radiotherapy dose delivered was heterogeneous due to differences in tissue densities and limits of planning capabilities. The use of CT imaging enabled an increase in precise delineation of both tumour and healthy tissues. Additionally, the development of conformal radiotherapy with three-dimensional planning techniques facilitated not only measurement of the dose and volume of radiotherapy delivered to tumours and organs at risk of injury, but also an understanding of the interaction between radiotherapy dose and toxicity.<sup>5</sup> The use of intensity-modulated radiotherapy and image-guided radiotherapy has also revolutionised the treatment of many malignancies, with substantial reduction in treatment-related toxicities and improvements in long-term outcomes.<sup>6-8</sup> With the advancements in techniques, complex targets can be treated at high doses with millimetre accuracy and steep dose fall-off to spare healthy tissues. Other developments include use of linear accelerators with onboard MRI or PET scanners, permitting greater tissue definition during treatment than without their use and allowing for adaptive therapy as tumour size or location changes during treatment (figure 2). Expanded parenteral applications for radiotherapy, such as radium-223 in prostate cancer,<sup>9</sup> theranostics, gamma knife radiosurgery, and

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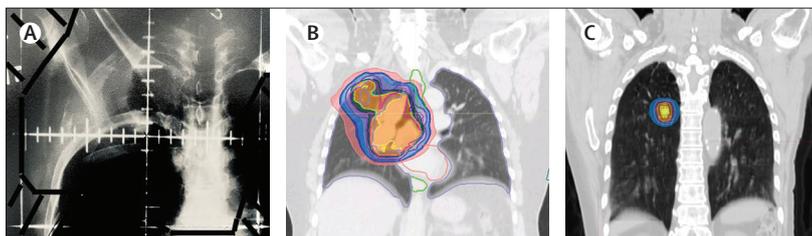
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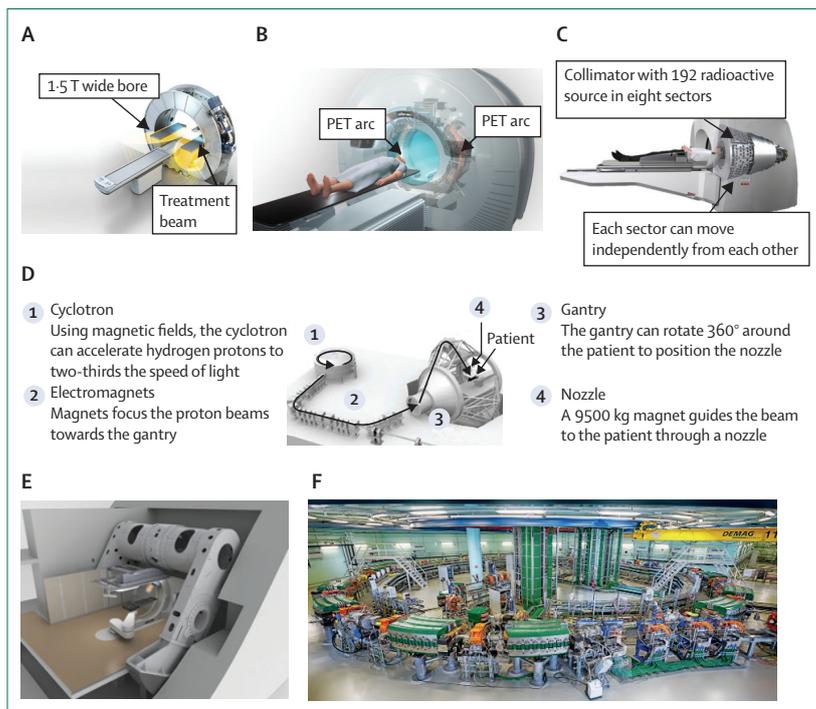
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### Search strategy and selection criteria

References for this Review were identified through searches of PubMed and MEDLINE for articles, including high quality reviews, reports of practice changing, and randomised trial data, from Jan 1, 1980, to Dec 31, 2020, with search terms such as “radiotherapy”, “charged particle therapy”, “3D conformal radiotherapy”, “intensity-modulated radiotherapy”, and “randomized trial”. Emphasis was placed on articles less than 10 years old. We organised new developments into topical areas, which then formed the basis for additional searches.



**Figure 1: The evolution of radiation therapy from two dimensional to stereotactic body radiotherapy**  
(A) Two-dimensional planning image quality is poor and treatment fields (the area inside the black line) are large; as planning and imaging techniques improved, treatment by intensity-modulated radiotherapy (B) and stereotactic body radiotherapy (C) techniques were enabled. The dark blue lines in (B) and (C) represent the planning target volume; the other coloured lines represent the different isodose lines.



**Figure 2: New types of radiotherapy treatment machines**

Different tumour locations and types are expected to benefit from these new treatment facilities.

(A) An MRI-containing linear accelerator; MRI-guided treatment is mostly applied in tumour areas with poor visibility on CT or an organ with motion. Reproduced with permission of Elekta (Stockholm, Sweden). (B) A PET-containing linear accelerator, a treatment of special interest when boost strategies to metabolic activity are prescribed. Reproduced with permission of Reflexion (Hayward, CA, USA). (C) Gamma knife treatment unit; an advance of the gamma knife technique with the steep dose gradient, and it is mainly used in brain metastasis. Reproduced with permission of Elekta. (D) The basic design of a cyclotron-based proton facility, often requiring multiple buildings. Reproduced with permission of IBA International (Louvain-la-Neuve, Belgium). (E) A depiction of a single room proton unit. Reproduced with permission of Mevion (Littleton, MA, USA). (F) A carbon ion facility. Charged particle therapy is of most interest when a steep dose gradient is needed to reduce the healthy tissue toxicity of an adjacent organ. Reproduced with permission of MedAstron (Wiener Neustadt, Austria).

imaged-guided brachytherapy techniques, have also expanded the radiation oncology arsenal. Examples of novel radiotherapy techniques are shown in figure 3; several of these techniques will be discussed in this Review.

Although most patients worldwide are treated with photon therapy, the use of charged particle therapy, including proton and carbon ion therapy, has substantially increased (figure 2). Charged particle therapy is characterised by steep dose falloff with a minimal exit dose beyond a specified target.<sup>10,11</sup> Treatment plans with charged particle therapy can often greatly decrease the exposure of healthy tissues to radiotherapy, potentially reducing short-term and long-term side-effects.<sup>12,13</sup> Decreased exposure to healthy tissues is especially important in the treatment of paediatric patients, in whom exposure of radiation dose to healthy organs can have detrimental long-term effects,<sup>12</sup> and when treating tumours in close proximity to crucial healthy structures (eg, head and neck tumours near the base of the skull).<sup>14</sup>

Currently, access to charged particle therapy varies widely, and criteria for its use in adult patients is an area of active research (table 1), with trials focusing on not only overall and progression-free survival, but also quality of life and cost-effectiveness. Although there are many potential benefits to charged particle therapy, it has several potential unique uncertainties<sup>15</sup> that might affect outcomes. To take advantage of the dosimetric benefits of proton therapy, accurate prediction of the range of the proton beam in tissue is needed, but this range can be affected by multiple factors, including, but not limited to, patient set-up, imaging, motion of both the target and surrounding organs, biological effects, and dose calculation uncertainties. Monte Carlo simulations can be used to assess some of these uncertainties.<sup>15</sup> Randomised data to support the efficacy of proton therapy is essential. For example, a randomised trial in locally advanced non-small-cell lung cancer did not show an improvement in toxicity with proton therapy compared with intensity-modulated radiotherapy.<sup>16</sup> In some countries, eligibility is restricted to individual photon-to-proton plan comparison, weighing the probability of healthy tissue complication between proton therapy and intensity-modulated radiotherapy techniques and estimating the short-term and long-term benefit of each. In other situations, access to proton therapy is driven mostly by financial means and patient insurance coverage. Randomised trials are ongoing (eg, NCT02603341, NCT01617161, NCT03801876, NCT01993810, NCT01893307, NCT02179086, and NCT03180502).

Although improvements in radiotherapy treatment planning and delivery have affected all patients treated with radiotherapy, one of the greatest impacts has been in the increasing use of hypofractionated radiotherapy, which uses fewer fractions of radiotherapy with a higher dose per fraction than conventionally fractionated radiotherapy (typically in doses of 1.8–2.0 Gy per fraction for conventionally fractionated radiotherapy). Hypofractionated radiotherapy was traditionally limited to palliative treatment, wherein the intent of treatment was to improve symptoms but not to cure. Single-fraction courses have been shown to be equally effective as multiple-fraction courses of radiotherapy in palliative treatment.<sup>17</sup> By contrast, definitive-intent radiotherapy is delivered in small daily doses over multiple weeks to deliver an effective tumouricidal dose, while minimising toxicity. The improvement of delivery techniques has facilitated the use of shorter courses of radiotherapy, with the aim of reducing treatment times and maintaining or improving outcomes from conventionally fractionated radiotherapy. For example, in patients with early-stage breast cancer receiving whole breast irradiation, multiple randomised trials have established the efficacy and safety of hypofractionated radiotherapy compared with conventionally fractionated radiotherapy,<sup>18–21</sup> and these regimens are recommended over conventionally fractionated radiotherapy.<sup>22</sup>

The most prominent example of hypofractionation, stereotactic radiosurgery or stereotactic body radiotherapy (SBRT), involves delivery of a full treatment dose over one to five treatments. Initially developed for the treatment of intracranial tumours, stereotactic treatment has been adapted for use in multiple other body sites, including thoracic, gastrointestinal, genitourinary, and osseous sites. Unlike conventionally fractionated or hypofractionated radiotherapy, SBRT, which is also known as stereotactic ablative body radiotherapy, is characterised by delivery of an ablative dose of radiotherapy to tumours. As will be discussed, stereotactic radiosurgery and SBRT have helped create entirely new indications for radiotherapy, and their role continues to expand with advances in systemic therapy.

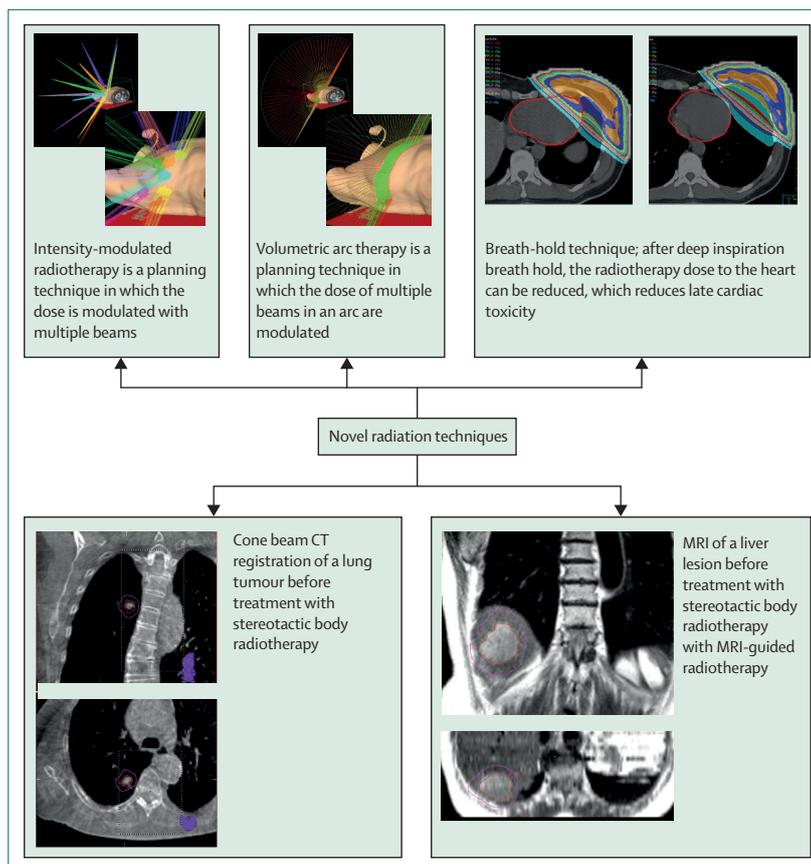
### New imaging: improved target definition, quantification of response, and novel therapies

Improvements in diagnostic imaging have enabled more precise identification of both target volumes and healthy tissue in radiotherapy treatment planning. For example, improvements in MRI have allowed a more complete assessment of intracranial disease burden than before. Coupled with advances in radiotherapy planning, this enhanced assessment of intracranial disease has led to a shift in the management of brain metastases, from whole brain radiotherapy to targeted treatments with stereotactic radiosurgery or hippocampal-sparing whole brain radiotherapy.<sup>23</sup>

Additional advances in radiotherapy treatment imaging include the development of four-dimensional (4D) CT, wherein CTs are acquired throughout the respiratory cycle, facilitating more precise measurement of tumour movement than conventional, or free-breathing, CT (video). 4D CT is particularly important in treatment of sites in the lung and liver, where respiratory motion can be quite substantial.

Imaging at the time of treatment delivery is also crucial (figure 4). Linear accelerators can be equipped with advanced on-board imaging, such as cone beam CT, which enable real-time identification of tumour position. MRI-linear accelerators, which combine an MRI unit with a linear accelerator, provide an additional layer of imaging assessment before treatment, which is particularly important in areas with organ motion and where tumour and healthy structures have similar tissue density, such as the pancreas or liver.<sup>24</sup> The development of these techniques enabled use of smaller planning treatment volumes than before their development, sparing larger volumes of healthy tissue.

With improvements in imaging and refinements in treatment planning and delivery, there is also an increased potential for heterogeneity between treatment centres. To mitigate for this potential, the European Organisation for Research and Treatment of Cancer has instituted Radiation Therapy Quality Assurance procedures. Consensus guidelines have also been developed for assistance



**Figure 3: Examples of novel radiotherapy techniques**

IGRT is a technique that enables precise delivery of radiotherapy by checking the set-up with imaging before treatment. Examples of cone beam CT IGRT (lung) and MRI IGRT (liver). The red lines represent the gross tumour volume and the pink lines the planning target volume. IGRT=imaging-guided radiotherapy.

with target definition by national societies.<sup>25</sup> International collaboration and guidelines are essential to overcome intercontinental differences in radiotherapy.

See Online for video

Advanced imaging techniques can also have an essential role in the assessment of treatment response and the need for additional therapies. For example, in gastro-oesophageal junction cancer, PET-CT to evaluate response to treatment after induction chemotherapy has been used for the selection of concurrent systemic therapy with radiotherapy.<sup>26</sup> The role of functional imaging for radiotherapy intensification or de-intensification is an area of ongoing research. Tumour heterogeneity can be visualised by functional MRI,<sup>27</sup> giving room to target specific areas of the tumour.<sup>28</sup> Other advancements include the development of rational dosing of radiotherapy based on imaging and prediction of treatment response.

### New biology: a changing role with systemic therapy

Developments in systemic therapy have also transformed the role of radiotherapy, enabling treatment with smaller radiotherapy fields, which has decreased

	Malignancy	Trial design	Number of planned participants	Study groups	Primary outcome	Secondary outcomes	Inclusion of cost-effectiveness analysis
NCT02603341	Breast cancer	Randomised phase 3	1278	Photon therapy vs proton therapy	Effectiveness of photon therapy vs proton therapy in reducing major cardiovascular events	5-year disease control, quality of life, association of radiation dose and quality of life, and cardiac toxicity; and 15-year disease-free survival, overall survival, and risk of secondary malignancies	Yes
NCT01617161	Prostate cancer	Randomised phase 3	400	Proton therapy vs IMRT	Compare bowel function at 24 months after radiation	Disease-specific quality of life at 2 years; cost-effectiveness at 2 years; radiation dose and bowel, urinary, and erectile function; biomarkers, or prostate cancer behaviour; and disease-specific and overall survival at 10 years	Yes
NCT03801876	Oesophageal cancer	Randomised phase 3	300	Proton therapy vs photon therapy	Overall survival and grade 3 or worse cardiopulmonary adverse events related to protocol treatment	Pathological response rate; grade 4 lymphopenia during chemoradiation, lymphocyte counts; locoregional failure; distant metastasis-free survival; progression-free survival; quality-adjusted life-years; and cost-benefit analysis	Yes
NCT01993810	Non-small-cell lung cancer	Randomised phase 3	330	Proton therapy vs photon therapy	Overall survival	Progression-free survival; adverse events; and cost-effectiveness analysis	Yes
NCT01893307	Oropharyngeal cancer	Randomised phase 2 and phase 3	360	IMPT vs IMRT	Phase 2: rates and severity of late grade 3–5 toxicity during 2 years after completion of treatment; and phase 3: progression-free survival	2-year disease-related outcomes; patient-reported outcomes; physician-reported toxicity; quality-adjusted life-years; cost-benefit analysis; and biomarker analysis	Yes
NCT02179086	Glioblastoma	Randomised phase 2	606	Photon radiotherapy randomised patients to standard dose photon radiotherapy or dose-escalated proton therapy vs dose-escalated radiotherapy	Overall survival	Compare dose-escalated photon therapy and dose-escalated proton therapy; toxicities; cognitive symptom severity; neurocognitive function; and lymphopenia	No
NCT03180502	IDH mutation, low to intermediate grade gliomas	Randomised phase 2	120	IMRT vs proton beam therapy	Change in cognition	Quality of life; symptoms; cognition measurement; incidence of adverse events; local control; overall survival; progression-free survival; dose-response relationship; and tumour molecular status	No

IMPT=intensity-modulated proton therapy. IMRT=intensity-modulated radiation therapy.

**Table 1: Ongoing trials for the comparative effectiveness of IMRT and proton beam therapy**

the potential short-term and long-term side-effects of radiotherapy. One example of this decrease in side-effects has been in Hodgkin lymphoma. This highly radio-responsive disease was historically treated successfully with radiotherapy alone, with treatment of the primary tumour and draining nodal basins. Although patients, often diagnosed in their first few decades of life, were in complete remission, they also had a risk of long-term morbidity due to the large radiotherapy fields. With integration of chemotherapy into treatment and the use of PET or CT to assess response, the care of patients has evolved. For example, patients with Hodgkin lymphoma who require treatment with radiotherapy are now typically treated with chemotherapy followed by radiotherapy to involved lymph nodes (termed involved site or involved nodal radiotherapy depending on planning techniques). Smaller volumes and lower doses are used than for

previous treatments, and thus the radiotherapy-related morbidity is decreased.

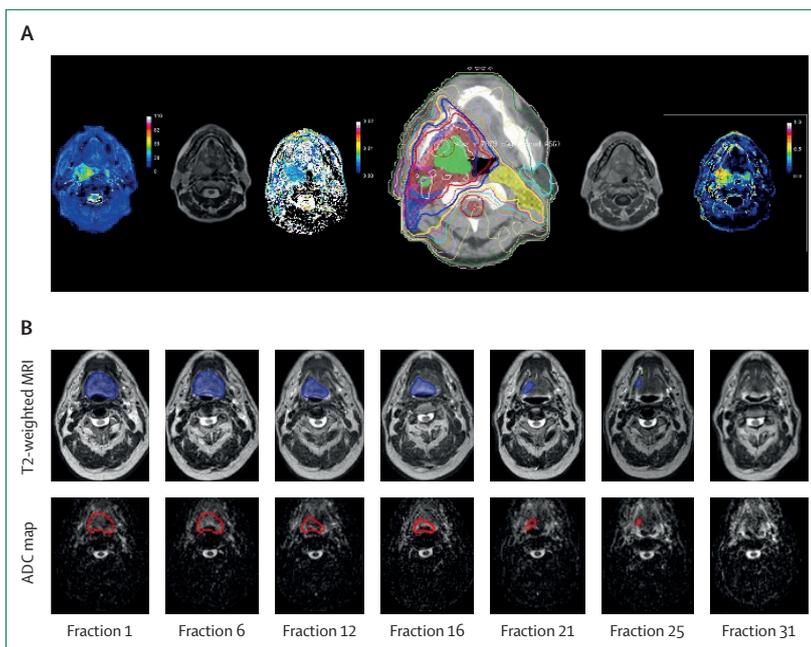
Immunotherapy<sup>29–31</sup> and targeted therapies<sup>32–34</sup> have also greatly improved patient outcomes, particularly for patients with locally advanced or metastatic disease. Studies have shown the potential for radiotherapy to stimulate or potentiate the immune response to checkpoint inhibitors,<sup>35–38</sup> and thus there is interest in combining radiotherapy with immunotherapy for therapeutic gain.<sup>39</sup> Reports of radiotherapy increasing response to checkpoint inhibition, even in so-called immunologically cold tumours, such as PD-L1-negative non-small-cell lung cancer,<sup>40</sup> microsatellite stable colorectal cancer,<sup>41</sup> and pancreatic cancer,<sup>42</sup> have additionally piqued the interest of clinicians and researchers in this area. Radiotherapy has both immunostimulatory and immunosuppressive effects that are independent of systemic therapy, including changes in tumour microenvironment,<sup>43</sup>

altered cytokine expression,<sup>44</sup> upregulation of transcription factors,<sup>45</sup> induction of cell death,<sup>46</sup> and promotion of antigen cross-presentation.<sup>47</sup> The optimal integration of radiotherapy with immunotherapy is an area of research, with preclinical trials highlighting optimal dose and fractionation and the underlying mechanisms of action, including stimulation of the production of type I interferon via the cGAS–STING pathway.<sup>48</sup>

Improvements in targeted therapy, particularly developments in tyrosine kinase inhibitors that have improved CNS activity, have also affected treatments.<sup>49,50</sup> For example, select patients with oncogene-drive lung cancers and brain metastases now receive CNS-penetrant tyrosine kinase inhibitors alone, with radiotherapy reserved for patients who do not respond to or progress through treatment. Additional study is crucial to identify potential side-effects of these approaches.

The potential interactions of radiotherapy with immunotherapy and targeted therapies is an area of ongoing research, particularly given the potential for increased side-effects when immunotherapy is delivered in proximity to radiotherapy. Clinicians should be aware of the potential risk of interaction of radiotherapy with these agents.<sup>51</sup> Knowledge of the mechanism of cancer inhibition of these drugs, medication half-life, and, consequently, the potential interaction mechanism with healthy tissue adjacent to the location of radiotherapy field should be used to establish how to sequence both treatments. The potential for overlapping toxicities, such as pneumonitis, between radiotherapy and systemic therapies needs to be considered. The decision on whether to directly overlap systemic therapies with radiotherapy or hold systemic therapies during treatment should be a joint decision between the treating radiation oncologist and the medical oncologist, considering the overall burden of disease, potential length of radiotherapy treatment course, and the overlapping risks of both treatments. Whenever possible, we encourage patients to enrol in clinical trials so that these decisions and their effects can be prospectively assessed.

Improved understanding of tumour biology has also led to interest in treatment de-escalation, with the aim of maintaining or improving upon previous outcomes and minimising toxicity. Appropriate selection of patients for de-escalation is crucial, as shown by the results of trials on de-escalation in human papillomavirus-related oropharyngeal squamous cell carcinoma. Human papillomavirus-related oropharyngeal squamous cell carcinoma is associated with more favourable outcomes than human papillomavirus-negative tumours,<sup>52,53</sup> to the extent that the most recent American Joint Commission on Cancer staging system downgraded the staging of human papillomavirus-related oropharyngeal squamous cell carcinoma.<sup>54</sup> However, in randomised trials by Gillison and colleagues<sup>55</sup> and Mehanna and colleagues<sup>56</sup> of cetuximab with concurrent radiotherapy versus cisplatin with concurrent radiotherapy there was a



**Figure 4: Advanced imaging technique examples in treatment planning and treatment response analysis** (A) Multiple complementary imaging methods used to define treatment volumes, including MRI, CT, and functional methods. Reproduced with permission from Clifton David Fuller, MD, PhD (MD Anderson Cancer Center, University of Texas, Houston, TX, USA). (B) MRI-based acquisition during a course of treatment to understand treatment response and adapt treatment volumes. Reproduced with permission from Clifton David Fuller. ADC=apparent diffusion coefficient.

significant reduction in tumour control with the use of concurrent cetuximab as compared with cisplatin. Additional randomised trials are ongoing (eg, NCT02254278), but these results highlight the challenges associated with treatment deintensification, even in groups with favourable outcomes. Additional studies to refine treatment subgroups will be crucial to these efforts.<sup>57,58</sup>

Genetic classification systems are also defining distinct subsets of disease that might warrant adjustments in treatment intensity or fields.<sup>59</sup> Molecular profiling of tumours has provided insights on sensitivity of tumours to radiotherapy.<sup>59–66</sup> For example, *KEAP1* and *NFE2L2* mutations have been identified as markers of radiation resistance in lung squamous cell carcinomas.<sup>67</sup> In hepatocellular carcinoma, mutations in *KRAS* and *TP53* have been significantly associated with risk of local failure (ie, tumour regrowth) after proton SBRT.<sup>68</sup> Similarly, in rectal adenocarcinoma, concurrent *KRAS* and *TP53* mutations have been associated with an insufficient response to neoadjuvant chemoradiotherapy.<sup>69</sup> Identification of these mutations, and others, might help to better predict those patients who are most at risk of local tumour progression and therefore facilitate the development of personalised radiotherapy prescriptions.

### New surgical cooperation: evolving framework of care

With the increase of multimodality treatment use, outcomes for many cancer patients have improved;

however, treatment intensification often comes with an effect on patients' quality of life. The need for treatment intensification to improve outcomes or de-intensification to improve quality of life differs between cancers. Substantial improvements in outcomes for breast, Hodgkin lymphoma, and head and neck cancer have resulted in exploring de-escalation of treatments. The balance and need of both surgery and radiotherapy is shifting with the changing effectiveness of the treatment options. For other tumour types, treatment intensification is being explored with the aim to increase the success of radical surgery and improve long-term outcomes (eg, pancreatic, gastric, or oesophageal cancer).<sup>70-73</sup>

The changing balance between surgery and radiotherapy is best highlighted by the development of modern breast cancer treatment. Systematic randomised trials,<sup>74-76</sup> done in the 1970s and 1980s, guided the development of breast cancer surgical techniques from the Halsted radical mastectomy to the simple mastectomy, and then to breast conservation therapy. The refinement of axillary nodal evaluation, from axillary lymph node dissection (ALND) to sentinel lymph node biopsy (SLNB),<sup>77-79</sup> has also reduced patient morbidity. In early-stage breast cancer, SLNB has largely replaced ALND, and in cases of lymph node metastases at SLNB, axillary radiotherapy has replaced ALND.<sup>79</sup> Oncoplastic techniques and modern radiotherapy principles are now improving cosmetic and functional outcomes for patients.

For head and neck cancer, the use of robotic surgical techniques has increased the use of surgery for treatment of oropharyngeal tumours, enabling resection of tumours that were previously deemed inaccessible due to potential morbidity. Assessment of the risks and benefits of each different approach will be crucial to ensure patients receive optimal combinations of treatment methods. For example, although some patients will be able to avoid chemotherapy after resection, others might still require both chemotherapy and radiotherapy, thereby increasing their overall burden of side-effects. The randomised phase 2 ORATOR trial<sup>80</sup> included patients with oropharyngeal squamous cell carcinoma who were randomly assigned to chemoradiotherapy or transoral robotic surgery with concurrent neck dissection. Oncological outcomes of both treatments were similar, but the toxicity profile of both treatments differed. Swallowing-related quality of life was improved with radiotherapy compared with surgery, although this was not a clinically meaningful difference. This study provides valuable information on the potential side-effects associated with both approaches.<sup>80</sup> Multidisciplinary assessment before the start of treatment will be essential for ensuring that patients' functional and oncological outcomes are maximised.

Finally, organ preservation represents an essential tool for patient wellbeing. Organ preservation is well established in anal cancer,<sup>81,82</sup> head and neck cancer,<sup>83</sup> cervical cancer,<sup>84</sup> and bladder cancer,<sup>85</sup> and there is

increasing interest in the potential for use in patients with oesophageal<sup>86,87</sup> and rectal cancer.<sup>88,89</sup> Studies on the use of organ preservation are highlighted in table 2.<sup>81-86,88-91</sup> Multidisciplinary response assessment is crucial to identify patients who are candidates for organ preservation, particularly when making the decision to omit resection in patients who are candidates for resection. The development of improved tools for response assessment will ideally allow the tailoring of treatment options for escalation or de-escalation of multimodality treatment, as appropriate.

### Special example: stereotactic radiosurgery or SBRT

The development and increasing use of stereotactic radiosurgery and SBRT in multiple disease sites has ushered in a new era of radiotherapy. There is established data for SBRT in nearly every cancer subsite that radiation oncologists treat, with indications ranging from early-stage disease (eg, in lung cancer) to locally advanced disease (eg, unresectable pancreatic cancer) and metastatic disease. These techniques are particularly appealing given the short course of treatment and small volumes treated, which correlate with a typically favourable side-effect profile. For example, in patients with early-stage non-small-cell lung cancer who are not candidates for lobectomy, SBRT is the standard of care,<sup>92</sup> and is associated with improved outcomes and reduced toxicity compared with conventionally fractionated radiotherapy.<sup>93</sup> Although there are no completed randomised trials comparing SBRT to resection, SBRT also compared favourably to lobectomy in a pooled analysis of participants in two randomised trials; however, as both trials did not have complete accrual, this analysis was limited by a small number of participants and a low number of events.<sup>94</sup> Additional randomised trials, including on the role of SBRT versus sublobar resection, are ongoing (eg, NCT02468024, NCT02984761, and NCT01753414).

One particularly exciting area is the potential role of stereotactic radiosurgery and SBRT in the treatment of metastatic disease. Prognostically, and perhaps obviously, a patient with two sites of metastatic disease might have a better outcome than a patient with 20, yet both are considered stage IV. It has long been known that particular patients with few sites of metastasis, such as adrenal metastases in T1-2N0 lung cancer,<sup>95</sup> liver metastases in colorectal cancer,<sup>96</sup> or pulmonary metastases in sarcoma,<sup>97</sup> can undergo aggressive local treatment of all sites of disease with long-term disease control. However, there has been controversy as to whether patients with more than one site of metastatic disease can also benefit from aggressive local therapy.

Molecular profiling studies have begun to define phenotypes of oligometastatic (low-volume metastatic disease at diagnosis) and oligoprogressive (low-volume progressive sites after systemic therapy) disease.<sup>98-100</sup>

Correlative studies on tumour genetic diversity and tumour evolution have lent support to the hypothesis that multiple distinct biological pathways influence oligometastatic and oligoprogressive disease in patients.

Advances in biomarkers, such as circulating tumour DNA,<sup>101,102</sup> have also led to improvements in assessment of disease burden. These advances are particularly important for patients who have received radiotherapy,

	Publication year	Study design	Population	Study groups	Organ preservation rate	Progression-free survival	Overall survival	Conclusions
<b>Laryngeal cancer</b>								
VA Larynx Trial <sup>83</sup>	1991	Randomised phase 3 trial	Stage 3 or stage 4 glottic or supraglottic squamous cell cancer	Induction chemotherapy for two cycles with radiotherapy starting with cycle three vs laryngectomy and postoperation radiotherapy	64% overall; of those requiring laryngectomy, 56% had thyroxine disease	Higher rate of local recurrence but lower rate of distant recurrence in chemoradiotherapy group than in the control	68% vs 68% (p=0.9846)	Larynx preservation is feasible without a detriment to overall survival in appropriately selected patients
<b>Anal cancer</b>								
Nigro and colleagues <sup>81</sup>	1974, and follow-up in 1983 and 1985	Case reports	At least 2 cm squamous cell carcinoma of the anal canal without distant metastases	Fluorouracil and mitomycin with concurrent radiotherapy (30 Gy in 15 fractions)	38 (84%) of 45 had complete response to chemoradiotherapy	7 (16%) of 45 had positive biopsy and ultimately recurred	89% overall survival at 50 months for patients with negative biopsy after chemoradiotherapy	Standard of care for anal squamous cell carcinoma became chemoradiation, with abdominoperineal resection reserved for patients with positive biopsy after treatment
James and colleagues <sup>82</sup>	2013	2 × 2 randomised factorial trial	Squamous cell carcinoma of the anus without distant metastasis	Radiotherapy with concurrent cisplatin and fluorouracil vs radiotherapy with mitomycin and fluorouracil, with or without two courses of maintenance cisplatin and fluorouracil	3-year colostomy-free survival was 68% with mitomycin and fluorouracil with concurrent radiotherapy	5-year disease-free survival was 69% with mitomycin and fluorouracil with concurrent radiotherapy	5-year overall survival was 79% with mitomycin or fluorouracil	Mitomycin and fluorouracil with concurrent radiotherapy are standard of care for anal squamous cell carcinoma
<b>Cervical cancer</b>								
Landoni and colleagues <sup>84</sup>	1997	Randomised phase 3 trial	Stage 1B and 2A cervical carcinoma	Radical hysterectomy with or without postoperation radiotherapy vs definitive radiotherapy	For tumours >4 cm, rate of pelvic relapse was 70% vs 53% (p=0.46)	5-year disease-free survival was 74% for both groups	5-year overall survival was 83% for both groups	Combination of surgery and radiotherapy has highest morbidity; tailor recommendations on the basis of patient and tumour characteristics
<b>Bladder cancer</b>								
Shipley and colleagues <sup>90</sup> and Efstathiou and colleagues <sup>85</sup>	1987; most recent follow-up in 2017	Phase 2 single-group trials or treated as per protocol	T2 to T4 muscle invasive bladder carcinoma	Maximal TURBT followed by concurrent chemoradiotherapy; salvage cystectomy recommended if less than clinical complete response or recurrence	5-year risk decreased from 42% in 1986–95 to 16% in 2005–13	5-year progression-free survival was 66%, 10-year progression-free survival was 59%	5-year overall survival was 57%, 10-year overall survival was 39%	Trimodality therapy is a potential alternative treatment for patients with muscle-invasive bladder cancer
<b>Oesophageal cancer</b>								
Bedenne and colleagues <sup>91</sup>	2007	Randomised phase 3 trial (259 of 444 participants were randomly assigned)	T3N0 to T3N1 thoracic oesophageal squamous cell carcinoma (90%) or adenocarcinoma	Neoadjuvant cisplatin and fluorouracil for two cycles with radiotherapy if response, randomised to surgery vs definitive chemoradiotherapy	NA	2-year local control was 57.0% with chemoradiotherapy vs 66.4% with trimodality therapy (p=0.0014)	2-year overall survival was 40% with chemoradiotherapy vs 34% with trimodality therapy (not significant)	Study was limited in that several patients were enrolled but not randomly assigned, and there was little clinical staging; recommend selective consideration for surgery
Stahl and colleagues <sup>86</sup>	2005	Randomised phase 3 trial	T3 to T4, N0 to N1, squamous cell carcinoma	Induction chemotherapy followed by chemoradiotherapy to 40 Gy and surgery vs induction chemotherapy followed by definitive chemoradiotherapy to 65 Gy	NA	2-year freedom from local progression was 64% with trimodality vs 41% with chemoradiotherapy (p=0.003)	2-year overall survival was 40% vs 35% equivalent	Surgery was associated with increased local control but did not improve overall survival

(Table 2 continues on next page)

Publication year	Study design	Population	Study groups	Organ preservation rate	Progression-free survival	Overall survival	Conclusions	
(Continued from previous page)								
<b>Rectal cancer</b>								
van der Valk and colleagues <sup>88</sup>	2018	Retrospective	T2 to T4, N0 to N2 rectal adenocarcinoma	Watchful waiting offered to patients with clinical complete response after neoadjuvant chemoradiotherapy	2-year incidence of local regrowth was 25.2% (n=213); 115 (78%) of 148 patients with local tumour regrowth required total mesorectal excision	5-year disease-specific survival was 94%	5-year overall survival was 85%	Close surveillance crucial with watchful waiting approach
Smith and colleagues <sup>89</sup>	2019	Retrospective	T2 to T4, N0 to N2 rectal adenocarcinoma	Watchful waiting offered to patients with clinical complete response after neoadjuvant chemoradiotherapy	82%	5-year disease-free survival of 75% (95% CI 62–90%) in watchful waiting vs 92% (87%–98%) in pathological complete response group	5-year overall survival of 73% (60%–89%) in watchful waiting vs 94% (90%–99%) for patients with pathological complete response	Although rectal preservation was high, overall survival was worse with watchful waiting; this approach should not be considered off trial

NA=not applicable. TURBT=transurethral resection of bladder tumour.

Table 2: Selected studies of organ preservation

	Number of participants	Histologies included	Median follow-up	Maximum number of metastases	Consolidative therapy	Concurrent systemic therapy	Median progression-free survival	Time to new lesions	Adverse events	Overall survival
Gomez and colleagues <sup>104,105</sup>	74	Non-small-cell lung cancer	38.8 months	3	Radiotherapy, chemoradiotherapy, or resection	Systemic therapy as per standard of care	14.2 months vs 4.4 months (p=0.001)	14.2 months vs 6 months (p=0.1)	Four grade 3 adverse events vs two grade 3 adverse events	41.2 months vs 17 months (p=0.02)
Iyengar and colleagues <sup>106</sup>	29	Non-small-cell lung cancer	9.6 months	6	Radiotherapy (SBRT or hypofractionated radiotherapy)	Maintenance chemotherapy	9.7 months vs 3.5 months (p=0.01)	Not reported	Four grade 3 adverse events vs two grade 3 and one grade 4 adverse events	Not reported
Palma and colleagues <sup>107</sup>	99	Breast, colorectal, non-small-cell lung cancer, prostate, and others	25 months	5	SBRT	Systemic therapy as per standard of care	12 months vs 6 months (p=0.001)	Not reported	29% worse than or equal to grade 2 adverse events vs 9% worse than or equal to grade 2 adverse events	41 months vs 21 months (p=0.09)
Phillips and colleagues <sup>108</sup>	54	Prostate	18.8 months	3	SBRT	None	Not reported vs 5.8 months (p=0.002)	Rate at 6 months was 16% vs 63% (p=0.006)	None	Not reported
Ost and colleagues <sup>109</sup>	62	Prostate	36 months	3	Surgery or SBRT	None	21 months vs 13 months (p=0.11)	Not reported	Six grade 1 adverse events vs no toxicity	Not reported

SBRT=stereotactic body radiotherapy.

Table 3: Randomised phase 2 trials on the role of consolidative radiotherapy in oligometastatic disease

as assessing response in previously irradiated fields can be challenging.<sup>103</sup>

Simultaneously, multiple randomised phase 2 trials on the use of radiotherapy in patients with oligometastatic disease have provided increasing support for the use of SBRT (table 3<sup>104–109</sup>). In these phase 2 trials, patients with low-volume metastatic disease were offered local therapy,

most often with SBRT, to their primary site and sites of metastatic disease. Significant differences in progression-free survival were reported, prompting the initiation of larger, phase 3 studies (eg, NCT03721341 and NCT03137771) with primary endpoints of overall, rather than progression-free survival. These ongoing trials will include patients receiving checkpoint inhibitors, which

is important as the previous phase 2 trials were done before routine use of immunotherapy. Although some of these studies allowed enrolment of patients with up to six metastatic sites, most patients enrolled only had one or two sites of metastasis. Randomised trials are now exploring the role of consolidative therapy in patients with more than five sites of metastasis (NCT03721341 and NCT03137771). Taken together, studies in consolidative therapy could portend a future where some kinds of cancer can be treated as a chronic disease, with SBRT being used periodically, and with some patients with metastatic disease being offered a chance at a cure through comprehensive target ablation at diagnosis. Defining oligometastatic disease is difficult, requiring assessment of multiple factors in addition to the number of sites of metastasis. A joint consensus document from the European Society for Radiotherapy and Oncology and American Society for Radiation Oncology discussed several of these criteria, including the site of metastases, feasibility of definitive local therapy, and systemic therapy options, all of which should be considered when defining oligometastatic disease and identifying appropriate candidates for aggressive local therapies.<sup>110</sup>

Stereotactic radiosurgery and SBRT are also utilised in palliative care; for example, showing excellent analgesic effect in patients with bone metastases.<sup>111</sup> SBRT has even been successfully used in benign tumours, such as trigeminal neuralgia,<sup>112</sup> and in non-oncological care, such as in patients with refractory ventricular tachycardia<sup>113</sup> and other cardiac arrhythmias, suggesting potential future use outside of oncology.

### Evolving indications: re-irradiation

Improved survival of patients with cancer has resulted in increased consultations for re-irradiation. In radiotherapy-naïve patients, dose constraints and corresponding toxicity profiles are robust. For re-irradiation, there is a paucity of data, which limits determination of firm guidelines or dose constraints. Therefore, efforts to guide clinical decision making in re-irradiation and determination of cumulative tolerated doses are based on small series and consensus recommendations.<sup>114,115</sup> When re-irradiation is considered, the decision to re-treat depends on multiple factors; the total dose of previous radiation, the anticipated dose for re-irradiation, and the time interval between radiotherapy courses should be assessed. The purpose of the re-irradiation is important (ie, whether the treatment is curative or palliative). Alternative treatment options that yield similar outcomes to re-irradiation or have a lower chance of toxicity than re-irradiation should also be investigated.

Knowledge of radiobiological principles is essential to understand the concept of dose tolerance in an organ. In general, organs are classified as serial or parallel organs. A serial organ, such as the spinal cord, will lose function if a small length of structure is sacrificed. By contrast, other organs (eg, liver or kidney) have redundancy built

in, and a particular proportion of the organ parenchyma (or functional subunits) can be removed while maintaining the organ function. The ability of serial organs to function after part removal generally implies that for serial organs a maximum tolerated dose is used, and for parallel organs the volume of the organ to a defined dose is used as a limit. Furthermore, if the radiation dose is higher than 2 Gy per fraction, the biological effective dose should be calculated.

Animal experiments have shown that re-irradiation of the spinal cord can be considered with caution if an appropriate interval is taken between treatments, indicating that there is potential for recovery over time.<sup>116</sup> Analysis in patients has showed that risks of myelopathy is small and depends on the cumulative dose, dose per treatment course, and time interval between treatments.<sup>117</sup> Single-fraction or multiple-fraction SBRT is often used for re-treatment of vertebral body metastases after conventional fractionation.<sup>118,119</sup>

Data for re-irradiation of different tumour sites are increasing. In locally recurrent rectal cancer, re-irradiation might be a potential treatment option with the aim to achieve a radical resection and improve long-term survival.<sup>120</sup> In locoregional recurrent lung cancer<sup>121</sup> and head and neck cancer,<sup>122</sup> re-irradiation is also considered. Ultimately, re-irradiation is associated with increased risks compared with an initial course of radiotherapy,<sup>123</sup> and the potential for tumour control should be balanced with the expected treatment-related toxicity. Shared decision making is of utmost importance when considering re-irradiation.

### Costs and gains of new treatment advances

In the past decades, radiotherapy technology has rapidly evolved, and many new radiotherapy treatment options have become available in high-income countries. Although these advances often reduce toxicity and improve patient outcomes,<sup>15,124</sup> they also have an increased financial cost.<sup>125</sup> Cost-effectiveness studies have attempted to objectively quantify the benefit of these treatments. For example, for paediatric patients who have medulloblastoma, proton beam therapy is associated with decreased rates of intelligence quotient decline, hearing loss, growth hormone deficiency, coronary artery disease, and secondary malignant neoplasm.<sup>126,127</sup>

For other radiotherapy developments (eg, hypofractionation and stereotactic radiotherapy), total fractions per treatment series are greatly reduced compared with conventional radiotherapy. These techniques demand more advanced image guidance than conventional radiotherapy, which requires more resources; however, the trade-off with reduction of visits shows a positive cost-effective result.<sup>128–130</sup> The cost estimations of SBRT and lobectomy for early-stage lung cancer were considered in a Markov model.<sup>131</sup> SBRT costs were €9234 and lobectomy costs were €10726, with quality-adjusted life-years of 16·35 years and 15·80 years, respectively.

This shows that SBRT has a higher probability of cost-effectiveness than surgery.

A new development in image-guided radiotherapy is MRI-guided radiotherapy. This technique has the advantage of improving target visualisation and adapting the radiation plan to the daily shape of the anatomy. These advantages increase accuracy and enable reduction of the planning treatment volume margins and consequently spare more healthy tissue than radiotherapy alone. MRI-guided radiotherapy is more costly than CT-guided radiotherapy. The number of patients treated on an MRI-linear accelerator is small due to the longer time required per fraction than a conventional linear accelerator, and the need for costly machinery and more trained personnel. With the ongoing improvements in this technology, the time per treatment fraction is expected to be reduced. However, treatment on the MRI-linear accelerator will probably remain more expensive than on a conventional linear accelerator. Future studies should investigate for which indications MRI-guided radiotherapy is a cost-effective treatment option.

These rapid innovations in high-income countries have resulted in a widening disparity between high-income countries and low-income and middle-income countries. The availability of radiotherapy facilities in several low-income and middle-income countries is insufficient. Worldwide, only 40–60% of patients with cancer are estimated to have access to radiotherapy facilities.<sup>132</sup> Access to radiotherapy for patients with cancer in low-income and middle-income countries is urgently needed to improve patient outcomes, both in the definitive and palliative setting. Although substantial investments are required for radiotherapy treatment centres, including a linear accelerator or Cobalt-60 machine, skilled personnel, and maintenance, these investments show substantial health and economic benefits.<sup>132</sup> Even in high-income countries, where capacity seems sufficient, radiotherapy facilities are often concentrated in cities. For people living in remote regions, access to radiotherapy can be incredibly challenging due to the long travel distance and need to commute for typically daily treatment visits. Expansion of radiotherapy access is essential to ensure that patients can benefit from radiotherapy and the technological advances described.

### Future for radiation oncology

As discussed in this Review, advances in radiotherapy could lead to the use of personalised radiotherapy prescriptions, individualised treatment based on accurate response prediction, an increase in organ preservation, novel indications in non-oncological diseases, increased use of particle therapy, and even more robust and adaptable responses to immunomodulatory therapies than before. Technological advances in radiotherapy delivery will continue in the coming years. We have highlighted potential advances in radiotherapy in appendix (p 1).

One exciting technological advance is ultra-high dose rate radiotherapy (FLASH). Conventional radiotherapy is typically delivered with dose rates around 0.03 Gy/s, over 2–7 min. But when radiotherapy is delivered in ultra-high dose rates (>40 Gy/s) in less than 1 s, minimal deleterious effect has been observed on healthy tissue. Data are sparse at this time,<sup>133</sup> but the potential to deliver high doses of radiotherapy with minimisation of toxicity has prompted substantial interest. Similarly, accumulating data for the use of therapeutic nanoparticles as radiosensitisers holds promise to maximise treatment response. Assessment of response is also poised to dramatically change, as the use of liquid biopsy or biomarkers with circulating tumour DNA and artificial intelligence provide new tools to assess patient disease burden.<sup>134</sup> These tools hold great promise to refine treatment by personalising cancer care.

These advances in cancer care provide great excitement and hope to our field. Although these technological advances are important, additional refinements in patient care are also incredibly important for patient wellbeing and outcomes during and after therapy. The development of artificial intelligence approaches, including virtual reality, has helped to prepare patients for the logistics of radiotherapy. For example, the Virtual Environment Radiotherapy Trainer system functions as a simulator for radiotherapy treatment planning and delivery and has improved both staff training and the patient experience.<sup>135</sup> Patient-reported outcomes research is also crucial to better understand the physical, emotional, and social side-effects of cancer therapies. As outcomes and survival continue to improve, continued follow-up to assess the long-term effect of all oncological therapies will be essential for maximising patient quality of life.

Finally, we would be remiss if we did not mention the effect of the COVID-19 crisis on oncological care. As we write this Review, COVID-19 has greatly impacted the care of current and future patients with cancer worldwide. Although some changes, including new opportunities for telehealth, hypofractionation, and remote management will probably benefit patients over time by expanding access to care, this period will probably have long-term effects on patient diagnosis and treatment, as well as on ongoing clinical trials. The cancer community will need to work together to overcome these challenges and ensure that patient outcomes continue to improve over the next 60 years.

#### Contributors

All authors contributed to writing and editing of this manuscript and have approved the final version.

#### Declaration of interests

We declare no competing interests.

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See Online for appendix

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