

# PERSPECTIVES

## TIMELINE

### Past, present, and future of radiotherapy for the benefit of patients

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**Abstract** | Radiotherapy has been driven by constant technological advances since the discovery of X-rays in 1895. Radiotherapy aims to sculpt the optimal isodose on the tumour volume while sparing normal tissues. The benefits are threefold: patient cure, organ preservation and cost-efficiency. The efficacy and tolerance of radiotherapy were demonstrated by randomized trials in many different types of cancer (including breast, prostate and rectum) with a high level of scientific evidence. Such achievements, of major importance for the quality of life of patients, have been fostered during the past decade by linear accelerators with computer-assisted technology. More recently, these developments were augmented by proton and particle beam radiotherapy, usually combined with surgery and medical treatment in a multidisciplinary and personalized strategy against cancer. This article reviews the timeline of 100 years of radiotherapy with a focus on breakthroughs in the physics of radiotherapy and technology during the past two decades, and the associated clinical benefits.

Thariat, J. *et al.* *Nat. Rev. Clin. Oncol.* **10**, 52–60 (2013); published online 27 November 2012; doi:10.1038/nrclinonc.2012.203

#### Introduction

Cancer is a major public health problem worldwide as it accounts for a quarter of all deaths and surpasses heart disease as the leading cause of death for people under the age of 85.<sup>1</sup> Moreover, management of cancer is a rising concern in an ageing population and is increasingly important in developing countries. Radiotherapy alone or, more frequently, given in association with surgery and medical treatments has been a major means of fighting cancer since the discovery of X-rays by Röntgen in 1895.<sup>2</sup> This article reviews the timeline of 100 years of radiotherapy with a focus on breakthroughs in the physics of radiotherapy and technology during the past two decades. As the ultimate goal of radiotherapy is to improve clinical outcomes of patients with cancer, the most relevant technological innovations will be illustrated in the light of the corresponding clinical achievements

through the results of randomized trials that have influenced evidence-based medicine.

#### Time of discovery

The late 19<sup>th</sup> century was a prestigious period for radiotherapy when three Nobel prizes were awarded for discoveries related to ionizing radiation.<sup>3</sup> In December 1895, Röntgen discovered X-rays (Timeline 1),<sup>2</sup> quickly followed, in June 1896, by Becquerel who discovered natural radioactivity<sup>4</sup> and in 1898, by Curie who isolated radium.<sup>5</sup> These three fundamental discoveries paved the way for the two main techniques of radiotherapy: teletherapy, using long source–surface–distance (SSD), and later called external-beam radiotherapy (EBRT); and brachytherapy, based on a short SSD, initially delivered with radium and later with 50 kV X-rays.<sup>6</sup>

This era was also successful when considering the rapid transfer from bench to bedside. The first patients with cancer were treated with radiation in 1896, that is 6 months after Röntgen's discovery, for gastric cancer and basal-cell carcinoma in France, America and Sweden.<sup>7–9</sup> The

harmful effects of radiation also became apparent very quickly,<sup>10</sup> and were taken into account to optimize the therapeutic ratio and stimulate radioprotection.

#### Kilovoltage era 1900–1940

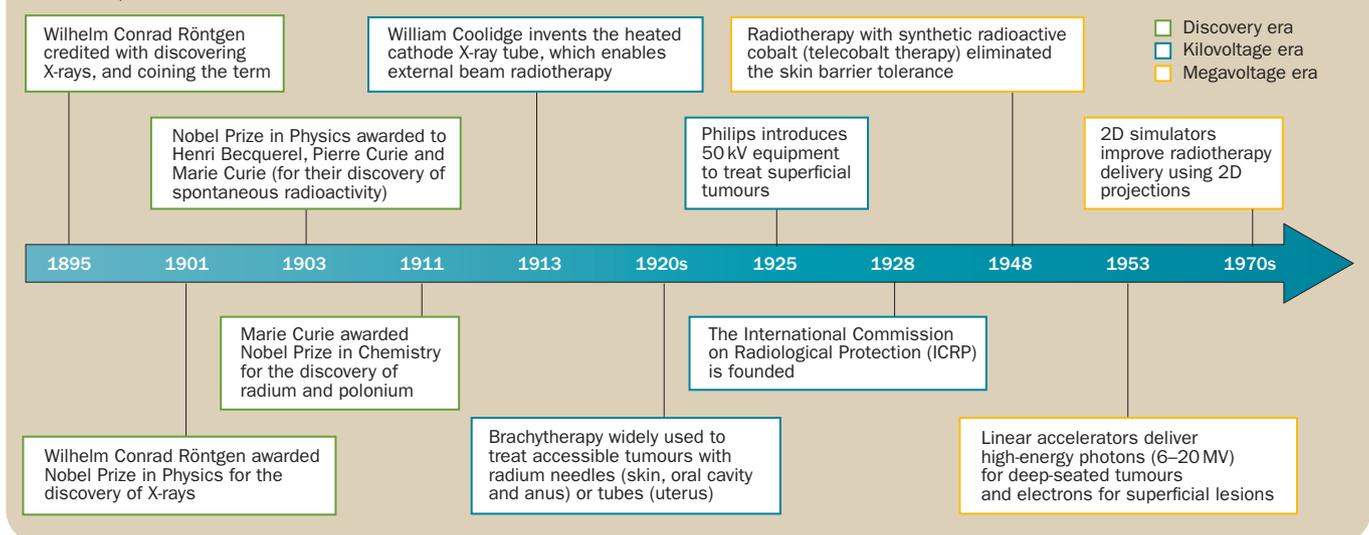
By 1913, manufactured radium tubes or needles and Coolidge tubes were designed to allow the routine use of radiotherapy in the fight against cancer.<sup>3</sup> Since that time, the aim of radiotherapy has always been, from a physical point of view, to deliver as close as possible to 100% of the dose in the target volume (gross tumour volume [GTV] or subclinical disease) and close to no radiation to the organs at risk (OAR). A major achievement made during that period was the capacity to measure the radiation dose using ionizing chambers<sup>11</sup> with the first accurate dose unit (the Röntgen unit) in 1932. With energies between 50 kV<sup>12</sup> and 200 kV, it was very difficult to deliver sufficient doses into deep-seated tumours primarily because of the associated unavoidable skin toxicity.

Cancer cure with EBRT was anecdotal and was limited to small superficial tumours (skin and vocal cord)<sup>13</sup> or to intrinsically radiosensitive cancers (Hodgkin lymphoma and seminoma);<sup>5</sup> and for brachytherapy to 'accessible' tumours (mobile tongue, anal or uterus cancers).<sup>14</sup> In the 1920s, radiotherapy seemed to be an oncology revolution, when for the first time it was possible to cure early stage laryngeal cancers without the mutilation of the permanent tracheostomy.<sup>15</sup>

The following fundamental laws, discovered at that time, remain the basis of today's practice. First, the different patterns of intrinsic radiosensitivity among cells and tissues were demonstrated by Bergonié and Tribondeau in 1906.<sup>16</sup> Second, the role of fractionation to create a beneficial differential effect between cancer and normal cells was discovered.<sup>17</sup> In 1934, Coutard proposed a fractionation scheme of 200 Röntgen per fraction, five times per week, which was converted into the standard contemporary 2 Gy/fraction scheme and, more recently, was well fitted with the  $\alpha/\beta$  model to describe its biological effect.<sup>18</sup> Third, in 1928, the International Commission on Radiological Protection (ICRP) was created to address the question of radioprotection;<sup>19</sup>

#### Competing interests

J.-P. Gérard declares an association with the following company: Ariane Medical Systems. See the article online for full details of the relationship. The other authors declare no competing interests.

**Timeline 1** | Early landmark discoveries in radiotherapy

the Geiger Müller tube was invented in 1928 to detect radioactivity.<sup>20</sup>

### Megavoltage era 1946–1996

Following the Nobel prize award to Irène and Frédéric Joliot-Curie for the discovery in 1934<sup>21</sup> of artificial radioactivity, and further to Jones and Cunningham's works,<sup>22</sup> cobalt 60 was adopted as an alternative source of high-energy  $\gamma$ -rays for teleradiotherapy, with a higher dose rate than could be achieved with radium. The first telecobalt unit was installed in Hamilton, Canada (Timeline 1). Over 1,000 machines were sold to hospitals worldwide in the following 10 years and these were used widely for 20–30 years.<sup>23</sup> The 1.2 MeV photon beam energy allowed, for the first time, cutaneous sparing and made the delivery of doses of up 45–60 Gy possible to deeply seated tumours without exceeding the tolerance dose of the OAR. Using this large-field EBRT was also considered to be an oncological revolution with the capacity to cure Hodgkin lymphoma, a disease that was previously considered to be an incurable cancer. The weakness of this robust and efficient technology was the use of radioactive sources with the risk of radiation exposure while managing waste sources,<sup>24</sup> which later led to its replacement by linear accelerators. Also, for radio-protection concerns, radium was gradually abandoned in favour of afterloading techniques.<sup>25</sup> The afterloading brachytherapy technique consists of two steps: positioning hollow vectors followed by loading of the radioactive sources—with manual handling or, better, remote mechanical teleloading.

Radar (klystron and magnetron) research led to microwave power tube technology and then to the construction of the first megavoltage linear accelerator (linac) X-ray machine in 1948.<sup>26</sup> The first medical linac built by Vickers was installed at Hammersmith Hospital in London in 1953.<sup>27</sup> Linacs were able to produce X-ray beams with a power between 6 MV and 20 MV, allowing the delivery of 60–70 Gy doses without exceeding the tolerance dose of OAR, even into very-deeply located tumours in the pelvis or thorax of obese patients.<sup>28</sup> Moreover, these linacs could also produce electron beams, well-suited for superficial targets (0.5–4.0 cm in depth).<sup>29</sup>

With the use of dedicated 2D simulators in well-individualized radiotherapy departments, it became possible to target tumours more accurately using 2D bony radiographic projections. During the same period, the introduction of treatment planning systems (TPS) using the first computerized algorithms<sup>30</sup> allowed more-accurate planning to further improve the accuracy of dose distribution. During this period, dosimetry dramatically improved with the use of new detectors, and the unit of the rad was replaced by the Gray (joules/kg).<sup>31</sup> Quality assurance, a method aimed at controlling treatment delivery and reducing deviations from a planned protocol, was introduced<sup>32</sup> to harmonize the accuracy of dose distributions with the help of national laboratories of dosimetry.<sup>31</sup> Since that time, radiotherapy has been a model for risk management and quality assurance programmes. Radiation oncologists

became important members of the multi-disciplinary oncology team and radiotherapy had become a standard curative treatment, as it dramatically improved local control, allowed conservative treatment and often improved survival.<sup>33</sup>

The International Commission on Radiation Units and Measurements (ICRU)<sup>19</sup> defined the concepts of GTV, clinical tumour volume (CTV), planning target volumes (PTV), and so on, which remain essential parameters of current treatment planning.<sup>34</sup> The concepts developed by ICRU are a basic, common language to harmonize the prescription, recording and—most of all—reporting of radiotherapy treatment.

Starting in the 1970s, randomized trials, mainly in patients with breast cancer, yielded high levels of statistically significant clinical evidence able to influence change in clinical practice.<sup>35</sup> For example, at that time, surgeons were reluctant to modify a radical mutilating surgery into a minimally invasive approach for the treatment of early stage breast cancer;<sup>36,37</sup> clinical practice changed owing to the results obtained from a randomized clinical trial, which demonstrated that, in such situations, conservative surgery combined with irradiation provides the same overall survival as a mutilating mastectomy.<sup>36,37</sup> Only a few months after these results were published the conservative approach had been adopted in most countries worldwide.<sup>38</sup> Rectal cancer also provides a good example of the relevance of randomized trials to optimize the use of radiotherapy and change clinical practice (Table 1).<sup>39–48</sup>

**Table 1** | Major randomized trials in operable, locally advanced rectal cancer without metastases\*

Study	Regimen	5-year local recurrence (%)	5-year overall survival (%)	Sphincter preservation (%)	Comments
Krook <i>et al.</i> <sup>39</sup> (1980–1986) <i>n</i> =204	Postoperative radiotherapy (45 Gy) vs postoperative concurrent chemoradiotherapy (45 Gy and 5-FU)	25 vs 13.5 ( <i>P</i> =0.03)	48 vs 58	50 vs 50	Postoperative concurrent chemoradiotherapy improves local control and survival; becomes standard treatment
Påhlman <sup>40</sup> (1987–1990) <i>n</i> =908	Surgery alone vs preoperative radiotherapy (25 Gy in 5 fractions)	25 vs 8 ( <i>P</i> =0.001)	55 vs 63 ( <i>P</i> =0.008)	44 vs 40	Postoperative death in experimental arm was reduced from 15% to 4% by reducing the volume irradiated ( <i>P</i> =0.001)
Marsh <i>et al.</i> <sup>41</sup> (1982–1986) <i>n</i> =284	Surgery alone vs preoperative radiotherapy (20 Gy in 4 fractions) small field (10×10cm)	36.5 vs 12.8 ( <i>P</i> =0.0001)	50 vs 56	48 vs 46	4 MV linear accelerator and small fields in the posterior pelvis reduce local recurrence without toxicity
Kapiteijn <i>et al.</i> <sup>42</sup> (1996–1999) <i>n</i> =1,861	Total mesorectal excision vs preoperative radiotherapy (25 Gy in 5 fractions)	11 vs 6 ( <i>P</i> =0.001)	63 vs 64	67 vs 65	Short course preoperative radiotherapy improves local control even with total mesorectal excision surgery
Lyon R96-02 <sup>43</sup> (1996–2001) <i>n</i> =88	Preoperative radiotherapy vs preoperative radiotherapy and XRB (85 Gy in 3 fractions)	11 vs 8	67 vs 67	44 vs 76 ( <i>P</i> =0.004)	Safe high-dose radiotherapy escalation with XRB enables improved sphincter and rectal preservation
CAO/ARO/AIO <sup>44</sup> (1995–2002) <i>n</i> =823	Postoperative concurrent chemoradiotherapy (45 Gy in 25 fractions and 5-FU) vs preoperative concurrent chemoradiotherapy (45 Gy in 25 fractions and 5-FU)	13 vs 6 ( <i>P</i> =0.006)	74 vs 76	71 vs 69	Preoperative concurrent chemoradiotherapy superior in terms of local control and early toxicity; becomes standard treatment
FFCD 9203 <sup>45</sup> (1993–2003) <i>n</i> =762	Preoperative radiotherapy (45 Gy in 25 fractions) vs preoperative concurrent chemoradiotherapy (45 Gy in 25 fractions and 5-FU)	16 vs 8	67 vs 67	50 vs 50	Preoperative concurrent chemoradiotherapy is superior to radiotherapy alone in terms of local control
MRC CRO7 <sup>46</sup> (1998–2005) <i>n</i> =1,350	Preoperative radiotherapy (25 Gy in 5 fractions) vs selective postoperative concurrent chemoradiotherapy (45 Gy and 5-FU)	10.6 vs 4.4	70 vs 68	63 vs 65	Confirmation of Kapiteijn <i>et al.</i> <sup>42</sup> Local control improved with preoperative radiotherapy vs postoperative concurrent chemoradiotherapy and with minimal radiation toxicity
ACCORD 12 <sup>47</sup> (2005–2008) <i>n</i> =598	Preoperative concurrent chemoradiotherapy (45 Gy in 25 fractions and capecitabine) versus preoperative concurrent chemoradiotherapy (50 Gy in 25 fractions and capecitabine and oxaliplatin)	6.1 vs 4.7 <sup>†</sup>	85 vs 83 <sup>†</sup>	74 vs 76	A sterilized operative specimen was observed in 13% of cases in first arm and 19% in second arm Local relapse at 3 years <5% with 50 Gy radiotherapy
STAR 01 <sup>48</sup> (2003–2008) <i>n</i> =747	Preoperative concurrent chemoradiotherapy (50.4 Gy in 28 fractions and 5-FU) vs preoperative concurrent chemoradiotherapy (50.4 Gy in 28 fractions and oxaliplatin)	NR	NR	79 vs 81	A sterilized operative specimen was observed in 16% of cases in both arms; oxaliplatin associated with higher early grade 3 toxic events and does not increase tumour sterilization

\*Clinical practice has changed from postoperative chemoradiotherapy to preoperative chemoradiotherapy with improvements in terms of local recurrence (36% to 5%), 5-year survival (48% to 76%), sphincter preservation (40% to 81%) and postoperative death (7–15% to 0.3%). However, these results might not be fully comparable because of stage migration over the past 20 years. <sup>†</sup>3-year rate. Abbreviations: 5-FU, 5-fluorouracil; NR, not reported; XRB, X-ray brachytherapy with Papillon techniques (50 kV).

If radiotherapy techniques are permanently improving, they are also permanently in association and/or competition with innovations achieved in surgical or medical treatments. In this regard, it was a considerable achievement of a clinical trial carried out in the Netherlands to demonstrate that even with modern rectal surgical dissection, preoperative EBRT still reduced local recurrence.<sup>42</sup> Other randomized trials were able to show that concurrent chemotherapy<sup>45</sup> and safe radiotherapy dose escalation<sup>43,47</sup> were improving clinical outcomes; at the current time local control rate is close to 95% and conservative surgery

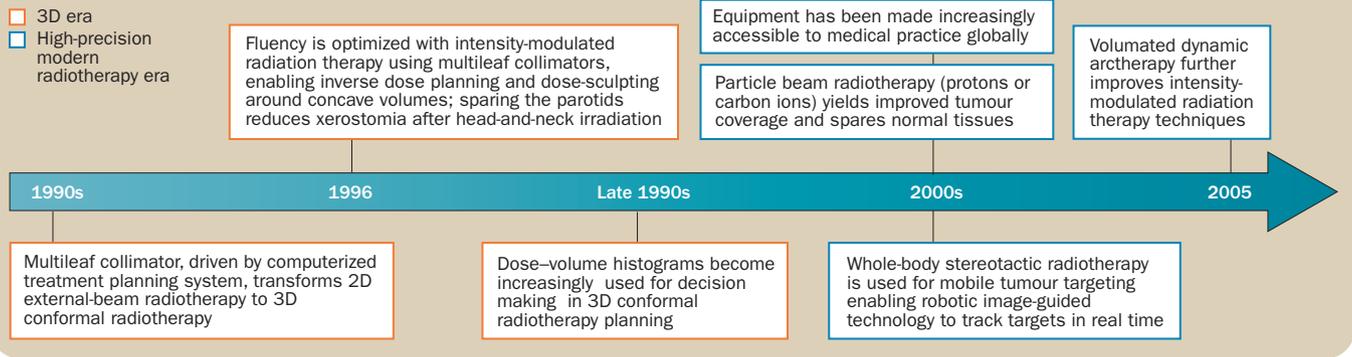
is carried out in 75% of patients with rectal cancer (Table 1).<sup>49</sup>

In other tumour types, such as anal carcinomas and choroid melanomas,<sup>50–52</sup> the benefit of radiotherapy seemed to be so obvious that patients could be spared from mutilation without the need for randomized trials to modify clinical practice.

### Computer-assisted 1996–2012 3D conformal radiotherapy

Hounsfield's invention of CT scans in 1971<sup>53</sup> translated into the clinic in the 1980s. With the use of computers in radiotherapy planning,<sup>54</sup> radiation delivery gradually

shifted from 2D to 3D planning. CT-based simulation and planning allowed better radiation dose distributions. The introduction of multileaf collimators, driven by computerized algorithms<sup>55</sup> and the new TPS<sup>56</sup> providing beam-eye-views,<sup>57</sup> rapidly revolutionized radiotherapy. It became possible to deliver the radiotherapy dose accurately with dose sculpting in 3D onto target volumes and avoiding OAR. Cumulative data on clinical tolerance and dose–effect correlations allowed the definition of specific tolerance doses of OAR using dose–volume histograms (Timeline 2).<sup>28</sup> CT-scans are now the first step of simulation in

**Timeline 2** | Modern advances in radiotherapy

routine radiotherapy practice. Prostate cancer is a good example of the clinical impact of better conformal distributions, which allow dose escalation (Figure 1).<sup>58,59</sup> 3D EBRT provided significantly better rectal protection in patients with prostate cancer treated with radiotherapy, as compared with 2D irradiation; it was possible to establish in a randomized clinical trial that dose escalation had a beneficial impact on biochemical and clinical outcomes for these patients.<sup>58–62</sup> Although EBRT using photons was the most-common technique assessed,<sup>63</sup> interstitial brachytherapy was also successfully investigated in randomized trials.<sup>64,65</sup> The trials of these techniques confirmed that high radiotherapy doses (78–80 Gy) significantly improved biochemical control and clinical outcomes compared to low radiotherapy doses (66–70 Gy).

### Intensity modulated radiotherapy

Based on a conformal EBRT approach, in the early 2000s, the next technical step forward consisted of the ability to further ‘modulate’ the photon beam intensity during fractions and to use inverse dose planning for treatment optimization using TPS.<sup>66</sup> This technical improvement allowed better conformation around the CTV and surrounding OARs and was termed intensity modulated radiotherapy (IMRT). IMRT was particularly useful in the treatment of patients with head and neck cancer, and was used to sculpt concave isodoses around the parotids. Parotid preservation could be performed using IMRT to prevent patients from experiencing severe xerostomia (systematically observed with conventional 2D radiotherapy), but with identical local disease control.<sup>67</sup> The PARSPORT randomized phase III trial recently provided a proof-of-concept for this strategy.<sup>68</sup> In addition, Zelefsky *et al.*<sup>63</sup> also showed an advantage of IMRT in patients with prostate

cancer who were treated with dose escalation up to 81 Gy without increasing rectal toxicity compared to the adverse effects observed after exposure to 70 Gy using 3D-conformal radiotherapy. In addition, recent improvements of IMRT technology have led to reduced treatment time using dynamic arc therapy.<sup>69</sup> Other derived techniques include tomotherapy, which uses a dedicated CT-scan unit and is well adapted to treat large volumes.<sup>70</sup> It is noteworthy that these techniques are used with conventional fractionation, but are also well adapted to deliver simultaneous integrated boost. With this approach, the boost dose is given during the same session of EBRT using reduced fields driven by the multileaf collimator, yielding higher doses to the GTV without increasing the overall treatment time.

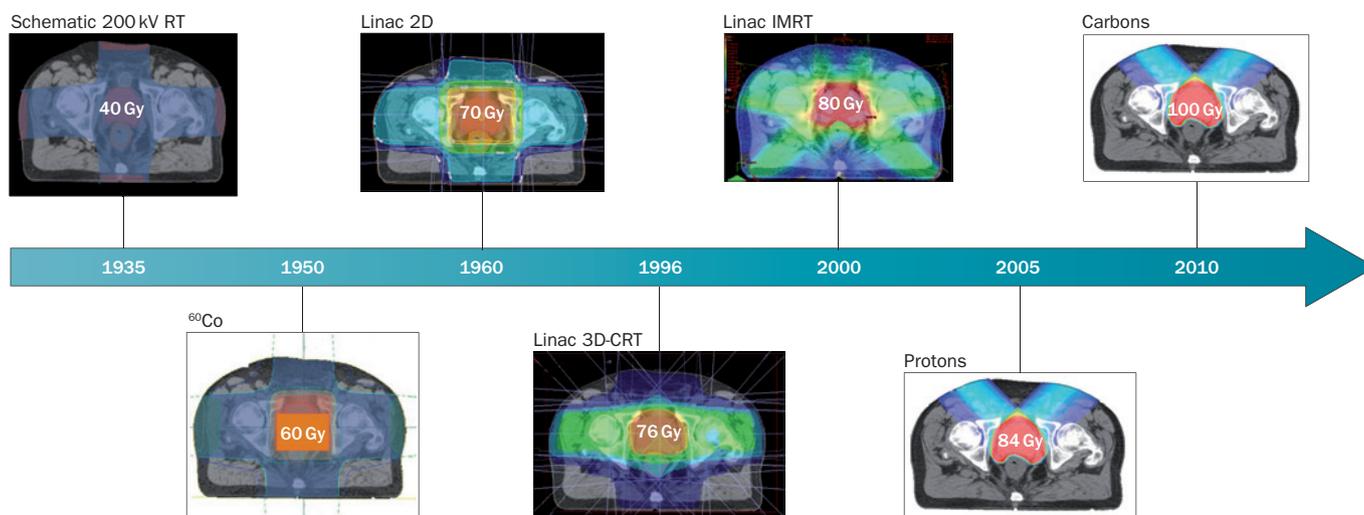
### Stereotactic radiotherapy

The first stereotactic devices were designed by Leksell for the treatment of intracranial benign or malignant lesions.<sup>71</sup> These devices called Gamma Units and, later, gamma knife use multiple <sup>60</sup>Co sources, non-coplanar small beams to deliver high doses into small target volumes in a highly accurate way using a stereotactic frame, which allowed hypofractionation in a single fraction. Such stereotactic radiotherapy is delivered today using dedicated machines.<sup>72</sup> Although intracranial lesions (including brain metastases) are the primary indications that can be treated using these systems, technical improvements in stereotactic body radiotherapy (SBRT) planning allow its use for extracranial lesions (such as those in the spine and mobile tumours). SBRT yields excellent results compared with surgery in patients with early stage lung tumours,<sup>73</sup> and patients are now randomly assigned to SBRT or surgery in clinical trials in operable patients. Outcomes of stereotactic ablative

radiotherapy in patients with potentially operable stage I non-small-cell lung cancer have been reported to be excellent.<sup>74</sup> SBRT is also extensively used as an aggressive treatment modality for oligometastases with a potential to prolong remission and good quality of life in some selected patients on the basis of number and size of metastases.<sup>75</sup> SBRT improvements are progressively changing the spectrum of metastatic disease into a chronic disease, especially for patients with lung and liver metastases that can be controlled in a large number of cases, with no or mild toxicity using a few SBRT fractions.<sup>76,77</sup>

### 4D radiotherapy

Patient, organ and tumour movements are the new technological frontier for radiotherapy. With the increasing use of highly conformal EBRT, it becomes possible to reduce the PTV by reducing geometric uncertainties during the radiotherapy course. Accounting for intrafraction and interfraction patient set-up uncertainties, tumour movements (including lung and liver movements with breathing), and tumour and patient contour changes in shape and volume over the 5–7 weeks of radiotherapy, requires an image-guided radiotherapy (IGRT) approach. IGRT can control changes in patient, tumour or organ position using kV control or cone beam CT offline or online.<sup>78,79</sup> Formal assessment of the clinical benefit of IGRT is under way. Adaptive radiotherapy (ART)—a form of IGRT that consists of ‘replanning’ and sometimes optimizing the treatment technique during the course of radiotherapy when clinically relevant<sup>80,81</sup>—aims to optimize the dose distribution depending on patient anatomy changes, and organ and tumour shape. ART has proven useful in a randomized clinical trial as it can provide dosimetric benefit with only one



**Figure 1** | Prostate cancer radiotherapy 1935–2010. Prostate cancer irradiation is a good example of the improvement of radiotherapy technology over the past decades. By increasing the beam energy and the precision of the targeting, it was possible to escalate the dose to the prostate without exceeding the tolerance dose of healthy tissues; allowing the move from palliative irradiation to curative treatment. Abbreviations: 3D-CRT, 3D conformal radiotherapy; IMRT, intensity modulated radiotherapy; RT, radiotherapy.

or two midtreatment replanning events. Preliminary clinical outcomes show functional recovery and preservation of disease control at 1-year follow-up and beyond with the use of ART.<sup>82</sup>

The radiotherapy industry has tackled the problem of moving targets by designing new machines, including stereotactic equipment such as the CyberKnife<sup>®</sup>, which has dedicated software to achieve real-time tracking of moving targets, and TrueBeam<sup>™</sup>, Verov<sup>™</sup>, and Novalis<sup>®</sup> among others, which allow online image guidance and various approaches of movement tracking.<sup>73</sup> The software and TPS algorithms are being constantly upgraded to improve the accuracy of dose delivery with the integration of time-related changes. To achieve such aims, continuous software optimization is an essential part of technological innovation.

### Brachytherapy

Brachytherapy with radioactive sources can use vectors (needles, plastic tubes or other applicators) placed within (interstitial) or close (plesio or endocavitary) to the target volume.<sup>83,84</sup> Taking advantage of the inverse-square law, brachytherapy offers an intrinsic conformal dose distribution, which facilitates dose escalation.<sup>85</sup> After a period of manual afterloading with low-dose-rate <sup>192</sup>Ir, remote afterloading with high-dose-rate image-guided brachytherapy is now common practice. Permanent implants using <sup>125</sup>I or <sup>103</sup>Pd seeds have also gained a major place in the treatment of patients with low-risk prostate cancer as an alternative to radical prostatectomy.<sup>86</sup>

X-ray brachytherapy (XRB; formerly called contact X-rays) using 50 kV X-rays was extensively used for the treatment of skin cancers and accessible tumours in the 1970s.<sup>87</sup> XRB<sup>43</sup> was used to cure small T1N0 rectal adenocarcinomas using a Philips<sup>®</sup> tube delivering doses to the tumour of 30 Gy in 2 min (Box 1). The Papillon 50<sup>™</sup> system reproduces similar dose distributions.<sup>88</sup> Interestingly, XRB can also be used intraoperatively with the IntraBeam<sup>®</sup> system to deliver a dose of 20 Gy into the tumour bed after local excision of small breast tumours. A randomized trial including 2,010 patients has shown equal 4-year local control and cosmetic results with intraoperative XRB or EBRT with 60 Gy in 30 fractions given over 6 weeks.<sup>89</sup> A similar intraoperative radiotherapy approach is also possible using electron beams (Box 1).<sup>90</sup> A randomized trial with positive results such as this one should lead to new development of intraoperative radiotherapy that can be used to safely increase the dose in a well-delineated target volume.

### Hypofractionation and personalization

All of the above-mentioned technological changes in EBRT and brachytherapy have improved the accuracy and conformality of radiotherapy. As severe toxic effects were kept below 5% when assessed at 3 or 5 years after treatment in several trials, a safe dose escalation seemed to be possible to increase both local control and organ preservation (Table 1).<sup>91</sup> Improved geographical accuracy is often associated with a reduction of the treated volume. A final consequence

of these technological improvements, along with a better understanding of the biology underlying the  $\alpha/\beta$  model, was to provide an opportunity to shorten the overall treatment time from a classical fractionation scheme that took 6–7 weeks to 3-week treatment schemes;<sup>92</sup> or reduce it even further to 3–5 fractions,<sup>93</sup> or even a single fraction using stereotactic radiotherapy. This trend toward hypofractionation, with the virtue of more-comfortable treatments for the patient and cheaper strategies for society, needs careful clinical evaluation through ongoing randomized trials.<sup>94</sup>

The vast set of different techniques and machines delivering X-rays, electrons, protons and so on has made it possible to individualize the type of irradiation that each patient receives. Some 20 years ago, most radiotherapy treatments were performed using isocentric, rather simple, two, three or four field techniques.<sup>95</sup> Now, it is possible to personalize the radiotherapy technique according to the different types of tumours and patients. Although standard three or four field treatment with 3D conformal radiotherapy is still used in more than 50% of patients, an increasingly large number of patients<sup>95</sup> are treated with IMRT, stereotactic radiotherapy, or ART, allowing the tracking of a mobile target.

Despite a trend towards a smaller treated tissue volume—sometimes a very small volume for patients treated with brachytherapy—large-volume treatment areas are also of interest when treating with total-body irradiation to control immunological reactions associated with bone marrow

transplantation, or total-skin electron irradiation to sterilize mycosis fungoides.<sup>96</sup> In many clinical situations, a specific technique of radiotherapy is a niche requiring dedicated equipment, staff and training as in stereotactic brain irradiation<sup>97</sup> or in image-guided brachytherapy.<sup>98</sup> Thus, some hyperspecialization seems to be inevitable in highly academic specialized centres.

### Protons and neutrons

In 1929, Lawrence, at the University of California in Berkeley, invented the cyclotron, a particle accelerator that is the forerunner of the machines used today in proton treatment facilities.<sup>99</sup> Wilson, as a physicist, citing the therapeutic potential of the Bragg peak, designed the Harvard cyclotron, which initiated proton therapy in 1946.<sup>100</sup> Meanwhile, neutron therapy was also used in radiotherapy. Taking advantage of a relative biological effectiveness close to three, fast neutrons were mainly used for the treatment of 'radioresistant' tumours. Some impressive instances of tumour control were achieved,<sup>101</sup> but late severe toxicities relating to sub-optimal dose distributions led to neutron therapy being abandoned.

### The future

#### Proton therapy

Proton therapy has seen spectacular developments in the past 10 years with about 70,000 patients treated in 30 centres in the USA, Asia and Europe.<sup>102</sup> Although no randomized trial has been performed, protons are considered to be a standard conservative treatment of ocular melanomas, especially in the posterior pole of the eye.<sup>52</sup> Eye preservation can be achieved in 90% of cases, with useful vision maintained in 50% of patients with choroidal melanoma based on worldwide experience on 30,000 treated patients.<sup>103</sup>

Hypofractionation (60 Gy in four fractions) in very-small tumour volumes (1–2 cm<sup>3</sup>) is efficient, with few toxic effects seen even in rare cases of local relapse within a previously irradiated organ.<sup>52</sup> Protons are also used to treat base of skull chordomas or chondrosarcomas with excellent results.<sup>104</sup> Developments in the radiation treatment of paediatric tumours aim to reduce the volume of OAR and normal tissues irradiated to avoid late sequelae or radiation-induced secondary cancers, because cured young individuals are at high risk of such adverse events.<sup>105</sup> Current limiting factors of treatment with protons are the size, heavy weight and cost of the machines. New

#### Box 1 | Brachytherapy modalities

- **<sup>192</sup>Ir afterloading** is the most frequently used brachytherapy modality. It can be performed with manual or, better, remote mechanical afterloading systems. The insertion of the radioactive source can be interstitial (such as for breast or anal canal tumours), but the most frequently used method is intracavitary (endoluminal) insertion into the vagina, uterus, bronchus or oesophagus. The dose can be delivered with low dose rate requiring hospitalization or increasingly with high dose rate on an ambulatory basis.
- **<sup>125</sup>I implant** is frequently used to treat early stage prostate cancer. The <sup>125</sup>I seeds are permanently implanted into the prostate under ultrasonography guidance.
- **X-ray brachytherapy (XRB; also called the Papillon technique)** does not use radioactive sources, but low-energy X-ray beam (usually 50 kV) with a short source–skin distance. One of the main advantages is that radioprotection problems are minimal and it is a fully ambulatory treatment delivering hypofractionated irradiation in three to six fractions over 3–4 weeks. It is used to treat accessible tumours under direct 'eye guidance'. Skin cancer of the face is an area that is frequently treated using XRB. It was the first radiotherapy technique to cure early stage rectal cancer. At the present time, intraoperative use of XRB is being developed in the treatment of early stage breast cancer as an alternative to other techniques of partial breast irradiation.

technological innovations are ongoing, such as those consisting of designing compact supraconducting synchrocyclotrons, which will weigh 25 tons (2.9 m of diameter) versus the 300 tons of isochrone cyclotrons.<sup>106</sup> The new facilities will be equipped with gantries to facilitate the beam orientation and an active spot-scanning beam system to better tailor the dose distribution to the 3D shape of tumours.<sup>107</sup> A very-low level of neutron contamination (less than 5%) will be a key element in radiation protection. Taking advantage of pulsed beam production, online proton imaging will facilitate the positioning and accuracy of the beam delivery.<sup>107</sup> Randomized clinical trials should probably be initiated to attempt to establish the improved OAR sparing and possible treatment time reduction that would be associated with treatment with protons compared with 3D conformal or IMRT using X-rays. The obvious dose distribution advantage of protons over X-rays should lead to a gradual replacement of X-rays with photons in many clinical situations (Timeline 2), as long as the machines can be installed at a reasonable price in hospital-based centres.

#### Carbon ions

<sup>12</sup>C have the same advantage as protons (in terms of their Bragg peak) for dose distribution with even less lateral diffusion in deep-seated tissues.<sup>107</sup> The benefit of treatments based on <sup>12</sup>C as compared with protons comes from an increased relative biological effectiveness in the region of the Bragg peak between 2 and 3.<sup>108</sup>

Such characteristics make treatment with <sup>12</sup>C especially attractive for radio-resistant cancers (sarcomas, melanomas and some adenocarcinomas).<sup>109</sup> The largest

clinical experience with <sup>12</sup>C is in Chiba (Japan) where, since 1994, approximately 6,000 patients have been treated using this method.<sup>109</sup> More recently, <sup>12</sup>C was used in Hyogo and Gunma (Japan), and Lanzhou (China).<sup>110</sup> In Germany, since 1998, treatment with <sup>12</sup>C has been undertaken at Darmstadt and, more recently, in the hospital-based facility of Heidelberg.<sup>111</sup> Potential indications that would benefit from treatment with <sup>12</sup>C are salivary gland (parotid) cancers, chordomas and skull base chondrosarcomas, sarcomas of bone and soft tissue, mucosal melanomas of the head and neck, adenoid cystic carcinomas and some adenocarcinomas (ethmoid sinus); in these tumours,<sup>109</sup> impressive local control rates have been achieved with acceptable levels of adverse effects. Randomized clinical trials are ongoing in Heidelberg and France to attempt to confirm these encouraging results. In Pavia (Italy), patients with base of skull tumours and childhood cancers are already being treated with protons and will be treated with <sup>12</sup>C in the coming months. As in the case for treatment with protons, the cost-effectiveness of <sup>12</sup>C therapy must be optimized. The use of other accelerator technology (superconducting synchrocyclotron S2C2, Linac booster, and so on) is under investigation. A helium beam with a mixed quality between protons and <sup>12</sup>C could also be a field of technological investigation.<sup>112</sup>

#### Efficacy and innovation

For a century, radiotherapy has seen continuous technological improvements, which have rapidly translated into better clinical results. The main goal was to improve the ratio between an optimal dose in the tumour and the lowest dose possible

in the OAR. After a long period of increasing the beam energy from 50–250 kV to 1.2 MeV (telecobalt) and 6–20 MV (linear accelerator), the recent period of technological research took advantage of the ‘computer revolution’ to adapt the radiotherapy beam delivery to a 3D conformal approach in complex volumes and moving patients, organs and tumours. The future, indeed almost the present, is the introduction of new particles including protons and probably ions ( $^{12}\text{C}$  and He) in routine practice. Throughout this history of technological evolutions, it is possible to stress three major advantages of radiotherapy in the global battle against cancer.

Firstly, radiotherapy is a curative treatment. Out of every 100 patients with cancer, 50 of them will be treated with radiotherapy.<sup>113</sup> Curative radiotherapy can be proposed in a majority of cancers. Cure is achieved using radiotherapy, often in combination with surgery and medical treatments, in 50% of patients who survive long term.<sup>113</sup>

Secondly, radiotherapy is a conservative treatment; the main merit of radiotherapy is its ability to sterilize a tumour without mutilation or body image alteration. Either alone or combined with organ-preserving surgery, radiotherapy can preserve the eye, larynx, breast, anorectum, urinary bladder and limbs, which is crucial to maintain a good quality of life. In an era of ageing populations, such a conservative, minimally morbid and curative approach is particularly attractive for elderly and frail patients.

Finally, radiotherapy is a cost-effective treatment. Taking France as an example, the total health cost for its 63 million inhabitants is €150 billion per year. The total cost associated with cancer (350,000 new cases per year) is €15 billion per year. Radiotherapy is used to treat approximately 200,000 patients (new or recurrent cases) per year; everything included (investments, running costs, salaries, transportation costs, and so on) it costs €1 billion, which is less than 10% of the total cancer budget.<sup>114</sup>

Taken together, these three advantages mean that radiotherapy is a permanent innovation that leads to dramatic clinical benefit. An overview of a century of radiotherapy shows that every time a technological innovation was brought into the clinic it rapidly translated into medical benefit for the patient. In 1903, the discovery of X-rays led to the first nonsurgical cure of skin cancer.<sup>5</sup> In the 1920s, using a higher-energy beam with the Coolidge tube larynx (vocal cord) carcinoma could be cured without

the mutilation of a total laryngectomy.<sup>15</sup> By the 1950s, Hodgkin lymphoma became a curable disease for the first time thanks to large-field radiotherapy (with moderate doses) using a Cobalt unit.<sup>8</sup> More recently, 3D conformal radiotherapy and IMRT have allowed the protection of patients with head and neck cancer from severe xerostomia,<sup>68</sup> and to control locally advanced prostate cancers,<sup>54</sup> using better ‘dose sculpting’. Already, proton beam therapy can cure melanoma of the eye, with good vision preservation, and is showing promising results in paediatric cancers.<sup>115</sup> The benefit of modern brachytherapy and  $^{12}\text{C}$  ions already seems to be very promising and hopefully ongoing and future randomized trials will confirm these early results.

### Multidisciplinary strategies

Although this article focuses on the technological improvements in radiotherapy, it must be strongly stressed that it is only a modest part of the global war against cancer. The primary way to win this war is prevention. Fighting against tobacco, alcohol excess, obesity, some infectious diseases, and so on, is the most-powerful weapon that could reduce by 20–30% the number of deaths by cancer. Screening for cervical, breast and colon cancer is also contributing to death reduction.<sup>116</sup> Most of the time, treatment is conducted using a multimodality approach where radiotherapy is often associated with surgery and/or chemotherapy<sup>117</sup> or molecular-targeted drugs. Cooperation between all these specialties is a key element of success and has been recently strengthened by the routine meetings of oncology multidisciplinary teams where radiation oncologists are a strong partner. With the growing role of molecular biology in the management of cancer, new classifications and subclassifications of tumours have emerged depending on the involvement of various cellular molecular pathways with proapoptotic or antiapoptotic actions. Tailoring the treatment to each of these new categories of cancer is becoming daily practice. Radiotherapy is actively participating in this ‘personalized medicine’ in two ways. First, in association with the multidisciplinary teams by choosing the right tumour to be irradiated according to these new molecular subcategories and, second, taking advantage of the vast set of different radiotherapy machines and techniques to optimally select the best technique and tailor the dose distribution to the tumour.

### Conclusions

Innovations in radiotherapy technology have yielded better patient care over time, demonstrated by randomized trials. This continuous effort of research would not be possible without the scientists, engineers, radiation oncologists and all the persons involved in the field of science and medical practice, in collaboration with all the other oncologists whose expertise, motivation and permanent ideal of progress has made this great story of radiotherapy a huge success to the benefit of patients with cancer.

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#### Acknowledgements

The authors acknowledge Pascale Martono, Adrian Plesu, Bastien Chanoux, Vincent Corvasce, Jerome Mandrillon and Karen Benezery for their help in making figures.

#### Author contributions

J. Thariat, J.-M. Hannoun-Levi and J.-P. Gérard researched the data for the article. J. Thariat and J.-P. Gérard discussed the article content and then wrote the manuscript with A. Sun Myint and T. Vuong. All authors edited the manuscript before submission.