Evolution of advanced technologies in prostate cancer radiotherapy

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Abstract | Conventional treatment options for clinically localized, low-risk prostate cancer include radical prostatectomy, external-beam radiotherapy (EBRT) and low-dose-rate brachytherapy. Advances in image-guided radiotherapy (IGRT) since the 1980s, the development of intensity-modulated radiotherapy (IMRT) during the 1990s and evidence from radiobiological models—which support the use of high doses per fraction—have developed alongside novel advanced radiotherapy modalities that include high-dose-rate brachytherapy (HDR-BT), stereotactic body radiotherapy (SBRT) and proton beam therapy. The relationship between the outcomes of and toxicities experienced by patients with prostate cancer treated with HDR-BT, SBRT and particle-beam therapy should provide urologists and oncologists an understanding of the continually evolving technology in prostate radiotherapy. On the basis of published evidence, conventionally fractionated EBRT with IMRT is considered the standard of care over conventional 3D conformal radiotherapy, whereas HDR-BT boost is an acceptable treatment option for selected patients with intermediate-risk and high-risk prostate cancer. SBRT and proton therapy should not be used for patients (regardless of disease risk group) outside the setting of a clinical trial. Finally, comparative effectiveness research should be conducted to provide a framework for evaluating advanced radiotherapy technologies by comparing the benefits and harms of available therapeutic options to optimize the risk:benefit ratio and improve cost effectiveness.

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Introduction

Prostate cancer is the most common noncutaneous malignancy and second leading cause of cancer death among men in the USA.[1] Since the 1970s, conventional treatment options for men with clinically localized, low-risk prostate cancer have included radical prostatectomy and radiotherapy techniques (Box 1), such as external-beam radiotherapy (EBRT) and low-dose-rate brachytherapy (LDR-BT). The outcomes of patients with localized (T1–T2) prostate cancer are directly related to local tumour control, even in spite of the patient having other high-risk features, such as high (8–10) Gleason score or serum PSA >20 ng/ml.[2] Dose-escalation strategies with conventionally fractionated EBRT[3] in use since the 1980s, as well as of conventional approaches for LDR-BT[4] (since 1987), have resulted in improved rates of local control, freedom from biochemical failure (FFBF) and patient outcomes. Moreover, the combination of LDR-BT and EBRT (so-called LDR-BT boost), with or without androgen-deprivation therapy (ADT), has proven beneficial in certain patients with intermediate-risk disease.

The delivery of radiotherapy has changed considerably since the 1980s. For example, the integration of various forms of image-guided radiotherapy (IGRT)[5–7] for EBRT and brachytherapy, and delivery with intensity-modulated radiotherapy (IMRT)[8–10] for EBRT planning, have enabled accurate dose escalation to improve outcomes and reduce toxicity. Furthermore, radiobiological models have suggested that prostate cancer cells are more sensitive to doses delivered in larger fraction sizes than in smaller, more frequent doses; normal tissues experience less toxicity with such doses.[11] This recognition heralded a considerable and growing interest in the clinical development of high-dose, short-course EBRT and brachytherapy approaches for men with prostate cancer. These developments have also occurred alongside technological advancements of other treatment modalities. We define a 'technologically advanced radiotherapy modality' as one with a significantly higher benefit:risk ratio than other radiotherapy modalities, with this benefit coming from the use of state-of-the-art IGRT, IMRT or both.

We believe three radiotherapy treatment modalities currently fit this description: high-dose-rate brachytherapy (HDR-BT), which is thought to have certain advantages over LDR-BT and conventionally fractionated EBRT, stereotactic body radiotherapy (SBRT; which is considered to have specific advantages over conventionally fractionated EBRT and brachytherapy) and particle beam therapy (proton therapy), which is thought to have certain advantages over photon radiotherapy (schedules juxtaposed in Figure 1). HDR-BT, SBRT and particle beam therapies are seldom mentioned in

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Key points

- Image-guided radiotherapy and intensity-modulated radiotherapy have been important in the development of novel radiotherapy modalities
- Similarly, radiobiological models, which support high dose per fraction delivery, have been critical for the introduction and evolution of high-dose-rate brachytherapy (HDR-BT), stereotactic body radiotherapy (SBRT) and proton beam therapy
- HDR-BT boost is a relatively well-established advanced radiotherapy modality that is suitable for certain patients with intermediate-risk and high-risk prostate cancer
- Patients of all risk groups can be offered SBRT and proton beam therapy, but only in the setting of a clinical trial because, to date, high-level evidence of efficacy and safety are lacking
- Comparative effectiveness research will provide a framework for evaluating advanced radiotherapy technologies by comparing the benefits and harms of the available options to optimize the risk:benefit ratio and improve cost effectiveness

risk-group-stratified comparative outcomes analyses (as defined by the National Comprehensive Cancer Network [NCCN],[12] Box 1) of conventional therapies because the studies using these modalities do not typically meet criteria for minimum number of patients treated, have limited follow-up durations, examine the radiotherapy in combination with other treatments (such as ADT)[13] or exclude patients with intermediate-risk and high-risk prostate cancer.[14] Although the toxic effects of conventional therapies have been comprehensively reviewed,[15] a detailed analysis of the adverse effects associated with these advanced radiotherapy modalities is not possible owing to limited follow-up times and the exclusive use of the Radiation Therapy Oncology Group (RTOG) scales to report adverse effects.

In this Review, we discuss the novel technologically advanced radiotherapy modalities for the primary treatment of men with prostate cancer. We review the advancements in IGRT and IMRT and their relation to the outcomes and toxicities of HDR-BT, SBRT and particle beam therapy to provide urologists and oncologists an understanding of the continually evolving field of technology in prostate radiotherapy.

Image-guided radiotherapy

One of the drawbacks of any radiotherapy modality is that the delivery of a high dose to achieve tumour control is limited by the dose delivered to nearby healthy organs (organs at risk). Moreover, prostate movement occurs during a radiotherapy session, which influences dosimetric coverage. The movement occurs both interfractionally (between two sessions)[16,17] and intrafractionally (during a single session)[18,19] and can be translational, rotational and deformational.[20,21] To account for these movements, an IGRT system obtains imaging coordinates of the target, healthy tissues or both before or during treatment, corrects for random and systematic errors that occur during treatment and helps to guide radiotherapy (that is, where the dose is delivered using brachytherapy or an EBRT method).

In theory, IGRT devices maximize the dose delivered to the tumour to improve patient outcomes and minimize the dose delivered to surrounding critical structures, decreasing adverse effects on the gastrointestinal and genitourinary systems. However, the use of IGRT systems varies widely in published studies.[10] IGRT systems were not used in randomized dose-escalation trials, and the NCCN[12] has only required IGRT be used when delivering any dose >78 Gy to the prostate since 2010. Retrospective studies have shown that such IGRT technologies can improve outcomes (in terms of FFBF[22–24] and local control)[23,24] and toxicity (in terms of late genitourinary[22] and late gastrointestinal[24] effects). However, some specialists have argued that there is no effect on cancer outcomes when higher doses per fraction are used.[25]

Developments to IGRT systems have been ongoing since the 1980s, alongside advances in other radiotherapy modalities (Figure 2). The use of particular IGRT systems is sometimes limited to specific radiotherapeutic devices; systems that acquire images before a session (2D and 3D IGRT) are more common than those that acquire images during a session (4D IGRT). Limitations of 2D and 3D systems include the inability to account for intrafractional motion, as well as interobserver and intraobserver variability (Table 1).[5–7] Additionally, all of these systems are limited by spatial resolution and their inability to delineate all cancer cells. Notably, most studies reporting the benefits of IGRT devices have been performed with photon-based radiotherapy, but not particle beam therapies. Although proton therapy is thought to minimize toxicity to normal tissues by minimizing the dose delivered to those tissues, if appropriate IGRT technologies are not used to guide the proton beam, the prostate can be geometrically 'missed' and delivery of the dose to surrounding tissues can occur. The appropriate IGRT systems for proton therapy are under investigation.

Cone-beam computerized tomography (CBCT) is one of the most popular IGRT systems used with EBRT (specifically, conventionally fractionated EBRT and SBRT). The convenience of CBCT over earlier systems (such as 2D electronic portal imaging device [EPID] with kilovoltage imaging) is that it can be automated and provides high-quality images of soft tissues with excellent spatial resolution in <1 min. CBCT is a technical tool that, if appropriately combined with positioning, correction and replanning protocols, can help obtain better (high-resolution) results.[26] By contrast, CT and transrectal ultrasonography (TRUS) are popular IGRT systems used for brachytherapy, as is MRI, which is popular for treatment planning.[27] Thus, one advantage of brachytherapy is that many of the IGRT systems used for EBRT are not necessary.

Intensity-modulated radiotherapy

In the early and mid-1990s, the most commonly used method to deliver conventionally fractionated EBRT was a four-field technique—having four radiation beams aimed at the prostate, in the anteroposterior and right-and-left lateral directions. At that time, there was no consensus on the optimal schedule or dose for treatment,[28] but dose escalation (to doses of 70–78 Gy) was shown to improve biochemical control in multiple phase III randomized controlled trials.[29–33] However, doses >78 Gy (to further improve outcomes) and hypofractionated

regimens require higher dose conformality—the ability to tightly shape the high dose region around the planning target volume to minimize the unnecessary irradiation of healthy tissues at high doses—than that which was possible with conventional 3D conformal radiotherapy (3D-CRT).[10]

IMRT was introduced in the early 1990s as a further refinement in the delivery of highly conformal radiation with 3D-CRT by increasing the dose delivered to the tumour volume and minimizing the dose delivered to surrounding organs. IMRT was made possible by the use of a multileaf collimator (MLC; Box 1) and advanced treatment planning calculation algorithms that optimize its position. Currently, a number of platforms exist to adjust the MLCs during treatment.[8] The dose distribution of IMRT is characterized by a concavity or invagination of the edge of the higher doses away from the rectum, rather than the straight edge through the rectum that is used in 3D-CRT.

IMRT is currently recommended over 3D-CRT for the radical treatment of localized prostate cancer in which an escalated radiation dose (>70 Gy) is required.[8–10] However, no randomized controlled trials that report outcomes and toxic effects have compared IMRT to 3D-CRT; among the retrospective studies that have compared the two modalities, outcomes have been similar.[10] With respect to toxicity, current evidence suggests that IMRT is superior to 3D-CRT on multiple scales, including the Short-Form-36 (SF-36)[34] University of California, Los Angeles Prostate Cancer Index (UCLA-PCI)[34,35] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Prostate (EORTC QLQ-PR25).[36] Notably, the RTOG scale has been shown to be insufficient for reporting late genitourinary and gastrointestinal effects because it does not integrate patient-reported outcomes and includes only five categorical toxicity grades (0–4) for two systems (genitourinary and gastrointestinal).[9,10] By contrast, the SF-36 and UCLA-PCI have up to six symptom subscores per system (for example, genitourinary symptoms include dysuria, nocturia, urgency and frequency), combined to make a grade from 0 to 100.[37] Furthermore, the degree of improvement of toxicity with IMRT over 3D-CRT is also under contention; although IMRT might be associated with lower rates of acute toxic effects,[38] the reduction might be minor.[39] Genitourinary adverse effect rates might be similar after 2 years for the two techniques,[40] but IMRT might be associated with higher rates of erectile dysfunction.[38,39]

IMRT is an advanced technology often used for the delivery of dose-escalated conventionally fractionated EBRT, hypofractionated EBRT and SBRT. The clinical implementation of IMRT involves many technical factors that can affect patient outcomes.[8] These factors include, for example, the planning system used, dose–volume constraints, type of IMRT delivery ('step and shoot,' tomotherapy or volumetric modulated arc therapy), treatment margins (prostate alone versus prostate and seminal vesicles) and dose per fraction and biologically effective dose (BED). Although some differences among the various forms of IMRT are apparent with different delivery systems, no one system has been determined to be superior clinically in terms of outcomes and toxicity.

Box 1 | Radiotherapy terms explained

Biologically effective dose (BED)
A conceptually more useful measure of biological damage to cells than physical dose that takes into account the α:β ratio, number of radiation fractions and fraction size.

Brachytherapy
A form of radiotherapy in which the radiation source is placed inside or next to the area requiring treatment. For prostate cancer, brachytherapy is typically given as either high-dose-rate (HDR-BT) delivered using a remote afterloading system (RALS) or low-dose-rate (LDR-BT) delivered using permanently implanted radioactive seeds.

Conventionally fractionated radiotherapy
A type of external-beam radiotherapy (EBRT) that is typically defined as a single 1.8–2.0 Gy fraction lasting 15 minutes per day, 5 days per week, for about 8 weeks, to a total dose of 76–80 Gy.

External-beam radiotherapy (EBRT)
The most common form of radiotherapy that includes conventionally fractionated EBRT, hypofractionated EBRT, SBRT and proton beam therapy.

Hypofractionated radiotherapy
A type of EBRT that is delivered as a single 2.1–3.5 Gy fraction lasting 15 minutes per day, 5 days per week, for 4 four weeks, to a total dose of 62–72 Gy.

Image-guided radiotherapy (IGRT)
An integral component of radiotherapy systems that obtains imaging coordinates of the target to treat and healthy tissues before or during treatment, detects and corrects for random and systematic errors that occur in patient setup and organ motion and increases accuracy and precision of the dose delivery.

Intensity modulated radiotherapy (IMRT)
An advanced form of high-precision radiation that conforms the treatment volume to the shape of the tumour.

Multileaf collimator (MLC)
A device made up of individual 'leaves' of a material with a high atomic number that can move independently in and out of the path of a particle beam to contour its shape to a tumour.

Prostate cancer risk group stratification
As per the National Comprehensive Cancer Network (NCCN),[12] prostate cancer is typically divided into three risk groups: low, (T1–T2a, Gleason score ≤6 and serum PSA <10 ng/ml), intermediate (T2b–T2c, Gleason score 7 and/or serum PSA 10–20 ng/ml) and high (T3a, Gleason score 8–10 or serum PSA >20 ng/ml).

Proton beam therapy
A type of EBRT that has a low incident energy and displays a spike at the tail end of its dose distribution (the Bragg peak) with essentially no dose beyond the end range. In theory, proton therapy spares the uninvolved tissues distal to the target.

Remote afterloading system (RALS)
Integral to HDR-BT, a RALS automatically deploys and retracts a single small radioactive source along the implant needle at specific positions, delivering ≥12 Gy per hour.

Stereotactic body radiotherapy (SBRT)
A type of EBRT delivered as a single 3.5–15.0 Gy fraction lasting up to 45 minutes per day, 5 days per week, for about 2 weeks, using IGRT and, sometimes, IMRT.

Radiobiology

In 2001, hypothesis-generating reports began to emerge that supported the rationale for high doses per fraction (for example, with HDR-BT and SBRT). Essentially, accurate and precise delivery of a high dose per fraction is thought to maximize prostate cancer cell death and minimize toxicity in normal tissues.[11] As the radiation dose increases, the number of surviving prostate cancer

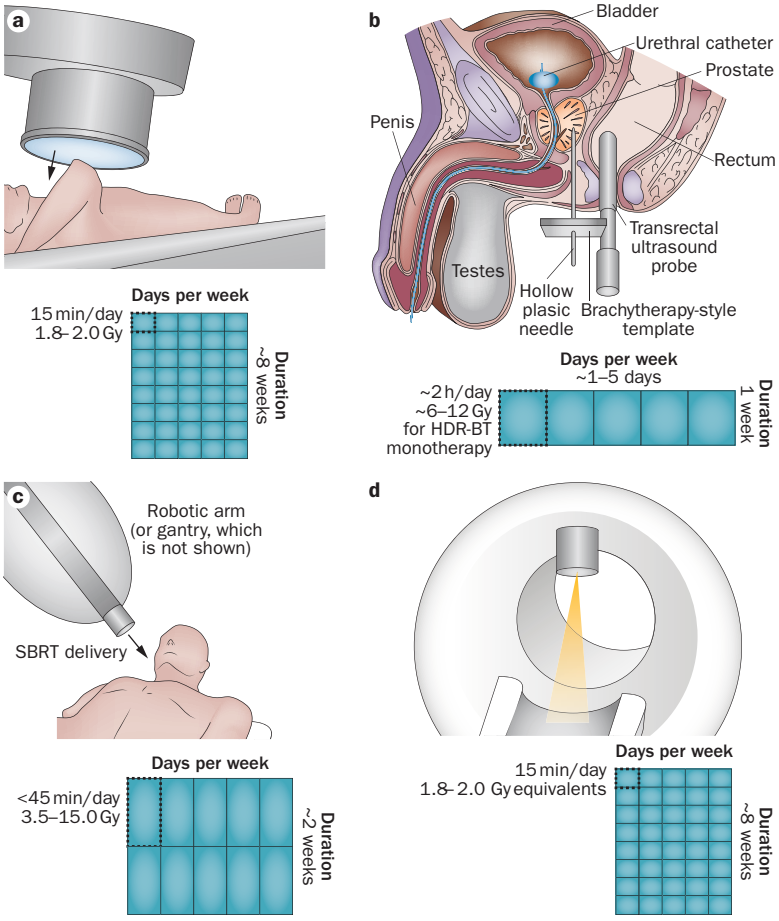

Figure 1 | Dose fractionation in advanced radiotherapy techniques. Currently, most men who receive EBRT for prostate cancer are treated with **a** | conventionally fractionated EBRT, which is typically defined as a single 1.8–2.0 Gy fraction lasting 15 minutes per day, 5 days per week, for about 8 weeks to a total dose of 76–80 Gy. Typical treatment schedules of advanced technologies—including **b** | HDR-BT, **c** | SBRT and **d** | proton beam therapy—vary compared with the conventionally fractionated EBRT schedule. Abbreviations: EBRT, external beam radiotherapy; HDR-BT, high-dose-rate brachytherapy; SBRT, stereotactic body radiotherapy.

cells decreases. However, this advantage is countered by the toxicity to neighbouring normal tissues. The α:β ratio estimates the effects of radiotherapy on various tissues and compares various dose and fractionation schemes. In this ratio, α describes the early slope of the radiation dose–response curve, for cells that die after one 'hit' of radiation and β describes the latter slope of the dose–response curve, for cells that require two radiation hits to die because of their ability to repair and repopulate. In simple terms, the α:β ratio is an index of sensitivity to radiation dose. A low α:β ratio (1–5) is characteristic of slowly proliferating cells that are more effectively killed by higher doses of radiation in fewer fractions (such as late-responding tissues that include connective tissue, bladder and rectal mucosa and muscles). By contrast, a high **α:β ratio (≥10) is characteristic of rapidly proliferat**ing cells that are more effectively killed by low doses of radiation in many fractions (such as early-responding tissues, which include skin, mucosa and most tumours). The ratio is used to calculate the BED, which is measure of biological damage to cells (Box 1): BED = $(nd[1 + d/(\alpha/\beta)])$, where n is the number of radiation fractions and d is the fraction size.

Radiobiological models based on clinical data suggest that prostate cancer has a low α:β ratio of ~1.5 Gy,[11] implying that the cancer cells are more sensitive to doses delivered in large fraction sizes than to doses of small fraction sizes. Indeed, the ratio value is lower than the 3–5 Gy estimated for late-responding tissues (connective tissue, bladder and rectal mucosa and muscles). If the α:β ratio for the tumour is lower than that for the normal tissues, increasing the dose per fraction would increase the BED for the tumour more than the BED for the normal tissues and, therefore, increase the therapeutic ratio.[41,42] Moreover, the cancer cells treated with high doses per fraction are thought to die by means that are not explained by typical radiobiological models, including lipid membrane phosphorylation.[43] Sample BED curves for α:β ratios of 1.5–10 for several HDR-BT, SBRT, hypofractionated EBRT and conventionally fractionated EBRT schedules are shown in Figure 3. Notably, however, for the normal tissues of organs at risk of adverse effects of treatment, the shape of the dose distribution matters; the different techniques have different capabilities in terms of conformality and, therefore, normal tissue sparing. The total BEDs of HDR-BT monotherapy, HDR-BT boost and SBRT studies (at an α:β ratio of 1.5) are listed in Tables 2 and 3, respectively.

Among conventionally fractionated EBRT regimens (that is, in 1.8–2.0 Gy fractions), the dose relationship seems to be essentially linear between 64 Gy and 80 Gy;[44] it has been hypothesized that to achieve 100% local control, doses of 86.5–95.5 Gy would be needed, depending on the risk category of the patient.[45] In other words, BED escalation to values of approximately 170–180 Gy is associated with improved outcomes (FFBF and locoregional control) for conventionally fractionated IMRT[46] and HDR-BT boost,[47] without an increase in toxicity.

High-dose-rate brachytherapy

LDR-BT with ^{125}I or ^{103}Pd seeds has been used clinically to treat localized prostate cancer since the 1970s. TRUS-guided LDR-BT became a standard treatment in the USA in the 1990s because it demonstrated improved outcomes and was less invasive than laparotomy-based surgical approaches.[48] However, the disadvantages of LDR-BT include postprocedure oedema, subsequent heterogeneous dose distribution, a high degree of operator dependency and an inability to deliver high doses over a short period of time.

To address some of these limitations, a TRUS-guided remote afterloading system (RALS) was introduced in 1980, capable of delivering a high radiation dose to the prostate. During the HDR-BT procedure, the RALS automatically deploys and retracts a single small radioactive source along the implant needle at specific positions, delivering ≥12 Gy per hour compared with 0.4–2.0 Gy per hour for LDR-BT.[49] The RALS also enables the physician to control the 'dwell position' where the source stops for a predetermined 'dwell time'. The source is then

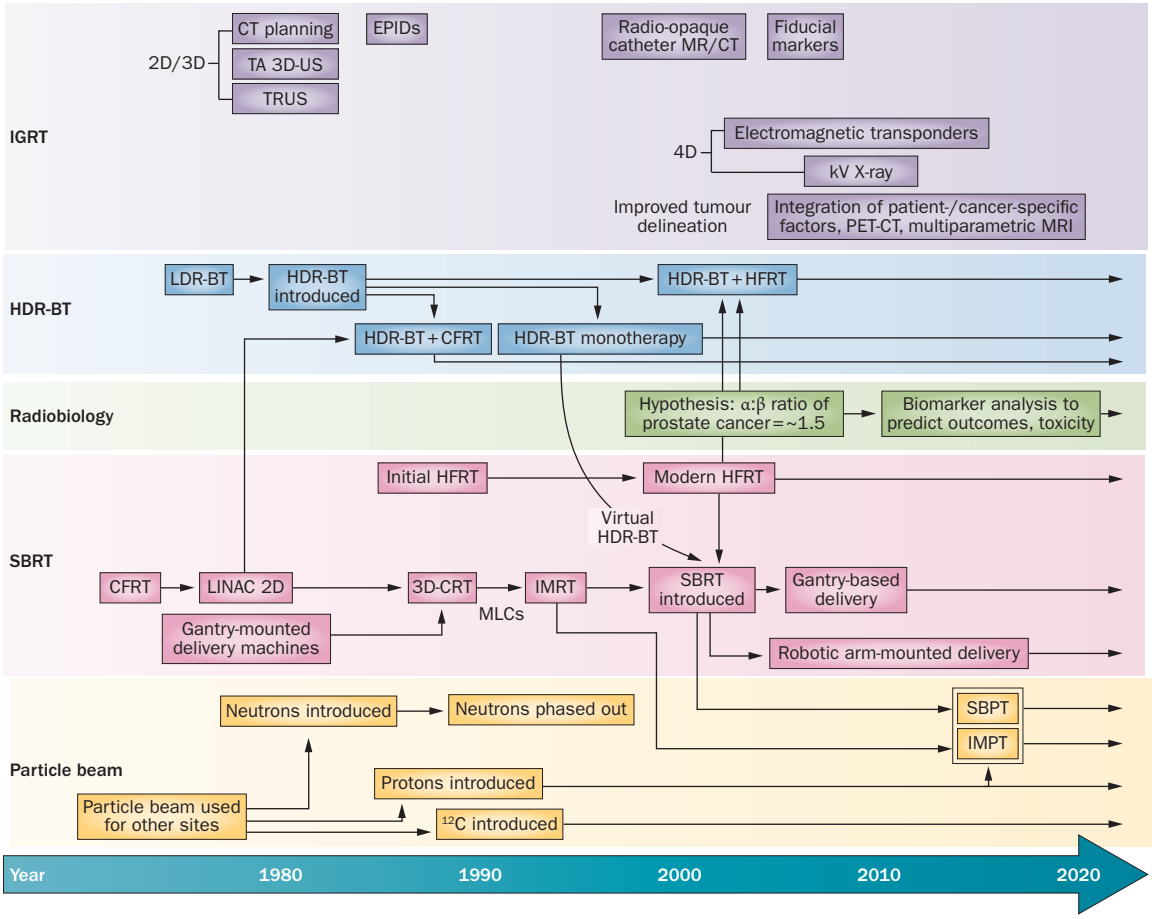

Figure 2 | The timeline and cooperation of radiotherapy advances. Advances in IGRT since the 1980s, the development of IMRT during the 1990s and radiobiological models (which support the use of high doses per fraction) have influenced the development of technologically advanced radiotherapy modalities, including HDR-BT, SBRT and particle beam therapy (such as proton therapy). Abbreviations: ^{12}C, carbon-12; 3D-CRT, 3D conformal radiotherapy; CFRT, conventionally fractionated external-beam radiotherapy; EPID, electronic portal imaging device; HDR-BT, high-dose-rate brachytherapy; IGRT, image-guided radiotherapy; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy; kV, kilovoltage; LDR-BT, low-dose-rate brachytherapy; LINAC, linear particle accelerator; MLC, multileaf collimator; MR, magnetic resonance; SBRT, stereotactic body radiotherapy; HFRT, hypofractionated external-beam radiotherapy; SBPT, stereotactic body proton therapy; TA, transabdominal; TRUS, transrectal ultrasonography; US, ultrasonography.

removed from the prostate, unlike with LDR-BT whereby the seeds are permanently deposited in the prostate.

IGRT with CT or ultrasonography should be used for HDR-BT and LDR-BT. IGRT is important for HDR-BT treatment planning to delineate the prostate and organs at risk because delivery of a high radiation dose to an incorrect volume would be associated with incomplete cancer treatment and toxicity,[50] and for LDR-BT because the movement of just a few seeds could significantly alter dosimetric coverage.[51] Indeed, ultrasonography-based planning of HDR-BT enables the procedure to be completed in 1–5 sessions, minimizing catheter displacement. Thus, the theoretical benefits of HDR-BT boost therapy that make it an advanced radiotherapy modality when compared with LDR-BT boost or EBRT monotherapy include the use of high doses per fraction, which result in higher tumour cell death and lower radiotoxicity, improved radiophysical parameters without the need for the complex IGRT systems needed for EBRT and patient convenience.[52,53]

The outcomes and toxicities of studies of HDR-BT are summarized in Table 2.[36,54–64] Many prospective studies have used HDR-BT as a boost therapy (with EBRT), but few have reported on HDR-BT monotherapy.[60] The 5-year FFBF rates for men with low-risk, intermediate-risk and high-risk prostate cancer have generally been >85%, 69–97% and 63–80%, respectively. These highly variable rates highlight the heterogeneity in the definitions of the risk groups, definitions for biochemical failure, follow-up times and other patient-specific characteristics—such as the use of androgen deprivation,[13] patient race[65] and post-treatment serum PSA nadir[66]—among the reported studies.[53] For patients receiving HDR-BT, for all the risk groups combined, the 5-year rates of cancer-specific survival, overall survival, local recurrence and distant metastasis are 99–100%, 85–100%, 0–8% and 2–12%, respectively. Dose-escalation studies of EBRT (that is, to doses of approximately 74–80 Gy in 1.8–2.0 Gy fractions) have helped determine a standard of care in prostate cancer

Table 1 | IGRT technologies for prostate cancer[5–7]

Device	Description	Advantages	Limitations
Before a session*			
EPIDs and digitally reconstructed radiographs	Planar images taken before each EBRT session aligned using skeletal anatomy	Widely available; No additional radiation compared; with planning CT	Cannot be used to visualize soft tissues, such as the prostate and rectum
Implanted fiducial markers	Seeds (1 mm in diameter) implanted transrectally into target before EBRT treatment course, used as part of other IGRT techniques	Visible on EPID and CBCT; Enable daily imaging and isocentre shifts; Newer markers have no image artefact during volume delineation; Reduce CT interobserver variability to <1 mm	Invasive procedure with risks similar to that of biopsy; Older markers cause image artefact during volume delineation, can require additional radiotherapy dose
Catheter with radio-opaque fiducial markers	Inserted into urethra before each EBRT session, used as part of other IGRT techniques	Visible on EPID	Repeated catheterization necessary; Sensitive craniocaudal position of catheter
Transabdominal 3D ultrasonography	Ultrasonography performed before each EBRT session	Enables visualization of structure outlines; No radiation	Causes temporary prostate displacement; Image quality limited by adiposity
Transrectal ultrasonography	Ultrasonography performed before brachytherapy session	Enables visualization of structure outlines; No radiation	Limited to HDR-BT and LDR-BT
CT-based systems (kV CBCT, kV CT on rails, MV CBCT and helical MV CT)	Volumetric radiographic imaging in radiotherapy room performed before each EBRT session	High-quality image acquisition of soft tissues; Excellent spatial resolution; Little time needed; Adaptive radiotherapy is possible	Some radiation (~5–15 cGy per image); Mesorectum difficult to visualize; Difficulty in discriminating prostate from fascia; Interobserver variability >2 mm
MRI on rails	Volumetric radiographic imaging in radiotherapy room performed before each EBRT session	Higher quality images than CT-based systems; No additional radiation	Limited data; Currently, no commercially available solutions; Requires large amount of space
During a session‡			
Electromagnetic transponders, stereoscopic X-ray with a robotic arm and kV X-ray systems	4D imaging systems that provide real-time EBRT tracking	Comparable isocentre position to fiducial markers (<2 mm)	Limited data

*2D and 3D IGRT. ‡4D IGRT. Abbreviations: CBCT, cone-beam CT; CRT, conformal radiotherapy; EBRT, external-beam radiotherapy (including conventionally fractionated EBRT, SBRT and proton therapy); EPID, electronic portal imaging device; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; kV, kilovoltage; MV, megavoltage; SBRT, stereotactic body radiotherapy.

radiotherapy.[29–33] Comparatively, for patients receiving 74–80 Gy in 2 Gy fractions, the reported rates of cancer-specific survival, overall survival, local recurrence and distant metastasis at 5 years are 95–100%, 83–95%, 0–20% and 1–12%, respectively. Comparing the outcomes of the dose-escalation studies to those of HDR-BT monotherapy and HDR-BT boost is difficult because the dose-escalation studies typically have a large number of patients ($n = 200–800$) to enable the reporting of outcomes with a stratification by risk groups and do not use more-advanced methods of treatment delivery, including volumetric modulated arc therapy and 4D radiofrequency tracking to increase normal organ sparing[67] and decrease intrafractional motion.[68]

Late RTOG grade 3–4 genitourinary toxic events have been reported at rates of 0–11%, and at rates of 0–3% for gastrointestinal toxic effects. On the basis of the large number of studies reporting long-term results with excellent tumour control and favourable toxicity profiles, HDR-BT boost is now a relatively well-established advanced radiotherapy modality for certain patients with intermediate-risk and high-risk prostate cancer.[50] On the other hand, a number of limitations preclude recommending HDR-BT monotherapy for prostate cancer outside the setting of a clinical trial, including limited follow-up duration (typically <4-year median follow-up time) and the use of only RTOG scoring to report toxicity without a detailed assessment of patient quality of life.[53]

Stereotactic body radiotherapy

SBRT was developed from the hypothesis that HDR-BT doses could be recapitulated from IGRT and gantry-mounted IMRT (which deliver conventionally fractionated and hypofractionated EBRT) or a robotic arm. In the 1980s and 1990s, hypofractionated EBRT was assessed in early clinical trials; however, the trials did not have an assumption that the α:β ratio was 1.5, and used old dose regimens (for example, to a total dose of 66 Gy [that is, <74 Gy]),[29–33] which would not deliver a sufficient dose to kill prostate cancer cells and might have led to more biochemical failures in patients treated with conventionally fractionated EBRT. Investigators of hypofractionated EBRT trials since 2001, by contrast, have tried to maintain a high BED (α:β ratio of 1.5) to kill prostate cancer cells while minimizing the BED (at α:β ratios of 3–10) for toxic effects. Trials comparing conventionally fractionated and hypofractionated EBRT were inconsistent in their results: the methods of early studies are not comparable to modern techniques, and the modern studies have rejected their hypotheses of superiority of hypofractionated EBRT.[69] Thus, although there is preclinical evidence to support a low α:β ratio for prostate cancer, multiple values have been reported (with most <3 Gy),[70] and the clinical data supporting the hypothetical evidence is lacking.[71] As of 2013, hypofractionated regimens are typically reserved for patients enrolled in clinical trials,[69] the theory of prostate cancer

cells having a low α:β ratio is one of the central supports for the efficacy of SBRT.[72]

In light of these results, the use of SBRT has increased since the early 2000s. SBRT has three major benefits that make it an 'advanced' radiotherapeutic modality compared with conventionally fractionated EBRT.[72] First, SBRT developed from the theory that HDR-BT doses could be recapitulated from IGRT and gantry-mounted IMRT or a robotic arm; thus, SBRT could deliver 'extremely' hypofractionated EBRT (also known as virtual HDR-BT). Second, the shorter treatment course of SBRT than conventionally fractionated EBRT (2 weeks versus 8 weeks) would be more acceptable to patients. Third, computational models have shown that changing to an SBRT schedule would decrease overall cost of treatment compared with the labour-intensive conventionally fractionated EBRT planning and delivery. Indeed, this is evident through the increased use of SBRT to treat men with prostate cancer in parts of the USA and Europe where access to radiotherapy centres is limited, even though long-term data about its efficacy and safety are not well established.

Efficacy and toxicity data from recent studies of SBRT are listed in Table 3.[73–81] FFBF rates for patients with low-risk, intermediate-risk and high-risk disease have all been ≥90% at up to 5 years. However, few studies have actually included men in the intermediate-risk and high-risk categories.[75,76,79] Among the studies included, ≤5% of patients experienced RTOG grade 3–4 gastrointestinal and genitourinary toxic effects.

SBRT (in particular, with robotic arm-mounted systems) is an example of a technology that seems to call for its own radiobiology, rather than the other way around. That is, the linear-quadratic model used to design of hypofractionation schedules is subject to its own uncertainties, particularly with respect to the upper limit of fraction sizes for which it remains valid.[82] This model is not comprehensive in all the pathways of cell death (for example, lipid membrane phosphorylation).[43] Thus, it is uncertain if the BEDs of SBRT can be accurately calculated with the equation presented in this Review.[83] Whether robotic arm-mounted SBRT is superior to gantry-based SBRT is not yet known; however, the conformality of a robotic arm-mounted delivery SBRT has been shown to be superior to gantry-mounted IMRT, although the dose fall-off seems similar in both plans[84] and neither has been proven to be more efficacious in terms of local control than the other. Outcomes from both gantry-mounted and robotic arm-mounted SBRT systems have been similar, with 2-year FFBF rates of 90–100% and 94–100%, respectively. However, detecting a statistically significant difference among FFBF rates at <5 years is probably impossible (particularly among patients with low-risk prostate cancer), and highlights a flaw among many SBRT studies. Although high-risk disease would be more likely to recur at an early time point, SBRT has been used primarily in men with low-risk prostate cancer, who typically have 5-year FFBF rates >85–95% after conventional surgery, robotically assisted surgery, conventionally fractionated

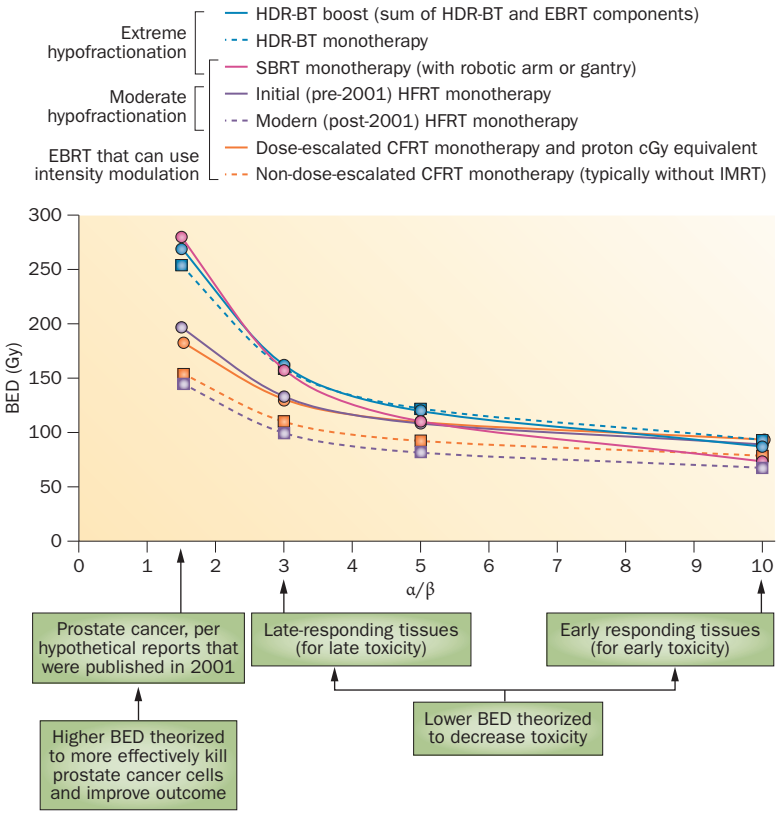

Figure 3 | A plot of BED curves for α:β ratios of 1.5–10 for several radiotherapy schedules. The following sample schedules are depicted: HDR-BT monotherapy (total dose of 54 Gy delivered in nine doses at 6 Gy), HDR-BT boost (total dose of 46 Gy delivered by EBRT in 23 doses at 2 Gy plus total boost dose of 19.5 Gy delivered in two doses at 9.75 Gy), SBRT monotherapy (total dose of 38 Gy delivered in nine doses of 9.5 Gy), hypofractionated EBRT (total dose of 70.2 Gy delivered in 39 doses at 2 Gy [modern schedule, post-2001] or total dose of 52.5 Gy delivered in 20 doses at 2.62 Gy [initial schedule, pre-2001]) and conventionally fractionated EBRT (total dose of 66 Gy delivered in 33 doses at 2 Gy for non-dose-escalated schedule; total dose of 78 Gy delivered in 39 doses at 2 Gy for dose-escalated schedule). In 2001, hypothesis-generating reports indicated that prostate cancer cells had a low α:β ratio of ~1.5, implying that the cells were more sensitive to large-fraction doses (which are used in HDR-BT, SBRT and hypofractionated EBRT). If the α:β ratio for the tumour is lower than for the normal tissues, increasing the dose per fraction would increase the BED for the tumour more than the BED for the normal tissues, increasing the therapeutic ratio. However, for the normal tissues of organs at risk, the shape of dose distribution matters, and the different techniques have different capabilities in terms of conformality and, therefore, normal tissue sparing. The dose conformalities of the different modalities are not depicted on this plot. Abbreviations: BED, biologically effective dose; CFRT, conventionally fractionated external-beam radiotherapy; EBRT, external-beam radiotherapy; HDR-BT, high-dose-dose brachytherapy; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy.

EBRT, LDR-BT and HDR-BT.[14] In summary, SBRT should be considered an experimental radiotherapy modality for all risk groups of men with prostate cancer and it should, therefore, only be used in the setting of a clinical trial.[72]

Particle beam therapy

Photon beams are the most common type of external radiation used clinically. Although the intensity of a photon beam decreases exponentially as it penetrates the patient (with a significant portion existing the distal

Table 2 | Selected studies of HDR-BT for prostate cancer: outcomes and toxicity

Study	*n*	Treatment (fractions)	BED at α:β of 1.5 (Gy)	Median follow-up time (years)	Actuarial follow-up time (years)	FFBF (%)			RTOG late grade 3–4 toxicity (%)	
						L	I	H	Genitourinary	Gastrointestinal
Prospective										
Demanes *et al.*[54] (2005)	209	HDR-BT (4)+EBRT (20)	190	7.3	7.3	90	87	69	8	0
Demanes *et al.*[57] (2009)	200	Arm 1: HDR-BT (4)+EBRT (20)	190	6.4	10	92	87	63	0	0
Demanes *et al.*[57] (2009)	211	Arm 2: HDR-BT (4)+EBRT (20)+ADT	190	6.4	10	92	87	63	0	0
Demanes *et al.*[60] (2011)	157	Arm 1: HDR-BT (6)	238	5.2	8	97	97	NA	NR	NR
Demanes *et al.*[60] (2011)	141	Arm 2: HDR-BT (4)	279	5.2	8	97	97	NA	NR	NR
Phase I/II										
Duchesne *et al.*[56] (2007)	108	HDR-BT (4)+EBRT (23)	166	6.5	5	NR	NR	NR	4	3
Kalkner *et al.*[58] (2007)	154	HDR-BT (2)+EBRT (25)	270	6.1	5	97	83	83	5	1
Tang *et al.*[61] (2006)	47	Arm 1: HDR-BT (4)+EBRT (23)	179	5	5	76	68	33	NR	NR
Tang *et al.*[61] (2006)	41	Arm 2: HDR-BT (4)+EBRT (23)	194	5	5	76	68	33	NR	NR
Tang *et al.*[61] (2006)	104	Arm 3: EBRT (33)	154	4.7	5	76	68	33	NR	NR
Vargas *et al.*[62] (2006)	67	Arm 1: HDR-BT (2–3)+EBRT (23)	211	4.9	5	69	69	69	8	0
Vargas *et al.*[62] (2006)	130	Arm 2: HDR-BT (2)+EBRT (23)	275	4.9	5	86	86	86	3	3
Phase II										
Galalae *et al.*[59] (2006)	122	Arm 1: HDR-BT (3)+EBRT (25)	198	5.3	5	59	59	59	NR	NR
Galalae *et al.*[59] (2006)	25	Arm 2: HDR-BT (2)+EBRT (25)	276	5.3	5	85	85	85	NR	NR
Galalae *et al.*[36] (2004)	593	HDR-BT (2–4)+EBRT (25)	297	5	5	96	88	69	NR	NR
Martinez *et al.*[63,64] (2003, 2010)	207	HDR-BT (2–3)+EBRT (23)	197–227	4.8	5	NR	85	75	12	1
Phase III										
Hoskin *et al.*[55] (2012)	108	Arm 1: EBRT (20)	156	7.1	10	60	62	70	4	2
Hoskin *et al.*[55] (2012)	110	Arm 2: HDR-BT (2)+EBRT (13)	215	7.1	10	100	89	80	11	0

Abbreviations: ADT, androgen deprivation therapy; BED, biologically effective dose; EBRT, external-beam radiotherapy; FFBF, freedom from biochemical failure; H, high-risk prostate cancer; HDR-BT, high-dose-rate brachytherapy; I, intermediate-risk prostate cancer; L, low-risk prostate cancer; NA, not applicable; NR, not reported; RTOG, Radiation Therapy Oncology Group.

side), a proton or carbon-12 (^{12}C) beam has low incident energy and displays a spike at the tail-end of its dose distribution (that is, the Bragg peak), with essentially no dose beyond the end range.[85] Consequently, proton and ^{12}C therapies spare the uninvolved tissues distal to the target and generally deposit a lower dose than photon beams to tissues proximal to the target.

Proton therapy was originally used to treat tumours in which a rapid distal dose drop-off was necessary to prevent toxic effects (for example, radionecrosis of the brain when treating uveal melanoma). To date, few studies of proton therapy for prostate cancer have been reported, with most studies using proton therapy to boost conventionally fractionated EBRT (Table 4).[32,86–89] The radiobiologically corrected doses of protons equivalent to those of photons would be expected to provide a similar therapeutic effect, but most studies have not correlated dose to outcomes. Moreover, fractionation schedules of proton therapy have not been influenced by radiobiological rationale that supports the use of high radiation doses per fraction with photon therapy—hypofractionated proton therapy and stereotactic body proton therapy for prostate cancer have not yet been attempted. Thus, comparing the published outcomes[32] and toxic effects[38,90] of proton therapies versus photon EBRT modalities (conventionally fractionated EBRT, hypofractionated EBRT and SBRT) is difficult.

Studies on other particle-beam therapies are also limited (Table 4). Neutron therapy was assessed in two trials (one in the 1980s, the other the 1990s);[91,92] although FFBF rates were improved compared with photons, high rates of toxicity have precluded the applicability of the method. Finally, experience with ^{12}C ions is promising (typically >83% for all risk groups at 5 years), but limited—only one institution has reported outcomes.[93–96]

Proton beam therapy is the most popular of the particle therapies. Since the 1980s, the early evidence of the benefit of protons was based on simple theories that normal tissues would receive less radiation. Proton therapy has been used around the world for cancers of the eye, skull base and spine, particularly in paediatric patients.[97] Indeed, in children, proton beam therapy has been shown to have a lower incidence of changes in vision, hearing and neurocognitive decline,[98,99] and incidence of second cancers, than other radiotherapy modality.[100]

Skull base and paediatric tumours, however, are rare, and the cost of building a proton cyclotron facility in the USA is upwards of US$200 million. Thus, manufacturers

Table 3 | Selected studies of stereotactic body radiotherapy for prostate cancer*

Study	*n*	System	BED at α:β of 1.5 (Gy)	Median follow-up time (years)	Actuarial follow-up time (years)	FFBF (%)			RTOG late grade 3–4 toxicity rate (%)	
						L	I	H	Genitourinary	Gastrointestinal
Phase I										
McBride *et al.*[73] (2011)	45	R	182–195	3.8	3	98	NA	NA	2	5
Boike *et al.*[79] (2011)	45	G	279–343	2.5	2.5	NA	100	NA	0	0
Phase II										
Mantz *et al.*[78] (2011)	66	G	221	3	3	100	NA	NA	NR	NR
King *et al.*[77] (2012)	57	R	182	3.2	4	94	NA	NA	4	0
Phase I/II										
Madsen *et al.*[74] (2007)	40	G	156	3.4	2	90	NA	NA	0	0
Tang *et al.*[66] (2008)‡	84	G	170	1.5	1.5	100	NA	NA	0	0
Katz *et al.*[75,76] (2010, 2011)	304	R	170–182	3.3	4	98	93	75	0	0

*All studies deployed the doses in five fractions. ‡Also Quon *et al.*[80,81] (2010), as part of the pHART3 study. Abbreviations: BED, biologically effective dose; FFBF, freedom from biochemical failure; G, gantry mounted; H, high-risk prostate cancer; I, intermediate-risk prostate cancer; L, low-risk prostate cancer; NA, not applicable; NR, not reported; R, robotic arm mounted; RTOG, Radiation Therapy Oncology Group.

of proton beam instruments look at the more-common cancers as a means to support these units.[97] Prostate cancer, because of its relatively high incidence, became an economic driver for the establishment of new proton facilities. Consequently, proton therapy was marketed on the internet at a highly advanced technology for prostate cancer.[101] The use of proton therapy for men with prostate cancer has been, therefore, highly scrutinized by physicians and policy makers.[97] Although new single-gantry proton facilities are being developed at a cost of $15–25 million, linear accelerators with IMRT are still much less expensive ($1–5 million). Thus, the superiority of protons compared with other modalities of radiotherapy must be established; advocates of proton therapy for prostate cancer who only cite theoretical benefits attract suspicion.[97]

A randomized control trial is currently ongoing in men with low-risk and intermediate-risk prostate cancer.[102] Currently, compared with HDR-BT and SBRT, proton therapy has comparable—but limited—evidence supporting its outcomes and toxicity. The benefit of proton beam therapy is likely limited to specific subpopulations.[103] Although proton therapy is novel and has theoretical dosimetric advantages, independent evaluation is still necessary to categorize the strongest and weakest indications for its use; indeed, prospective clinical trials are necessary to compare proton therapy to photon IMRT.[104] Moreover, proton therapy is in the midst of a significant technological transition, from passively scattered to actively scanned beams. Although advancements in proton therapy (unlike SBRT) have not been spurred by the expanded use of IMRT and IGRT, planning studies suggest that intensity-modulated proton therapy (IMPT) will be superior to state of the art IMRT in patients with advanced-stage prostate cancer,[105] but might not provide added benefit in early stage disease.[106] Finally, proton therapy might be used in a stereotactic fractionation regimen, but no clinical series currently support this hypothesis.

Clinical perspectives

Multiple factors can drive the choice of (or preference for) a given technology and the onus lies with clinicians to help patients make informed decisions for the most appropriate treatment modality. To that end, comparative effectiveness research (CER) will help personalize care for men with prostate cancer. Informally, CER is defined as an assessment of all available options for a specific medical condition, with intent to estimate effectiveness in specific subpopulations.[107,108] The contemporary concept of CER is to incorporate all available data to direct practitioners to optimal patient-specific treatment decisions. CER has become an essential component of prostate cancer research to provide a framework for evaluating advanced radiotherapy technologies by comparing the benefits and harm of available diagnostic, prognostic and therapeutic options to optimize the risk:benefit ratio and improve cost effectiveness.

Health policy

The push for CER is largely focused on changing health policies at the group level; that is, to have an overseeing body set guidelines for academic institutions and private practices on the appropriate use of individual technologies. Although the use of advanced radiotherapy technologies is increasing, the real-world effectiveness of these advanced technologies compared with standard technologies as delivered in a usual-care setting (such as community hospitals or rural areas) has yet to be determined. For example, the use of IMRT in the USA increased from 0.15% in 2001 to 96% in 2008, despite a lack of studies comparing the nongastrointestinal toxic effects and disease control with 3D-CRT.[38] Furthermore, since 2007, multiple proton beam facilities have opened, with advertising about the potential benefits of protons is leading to its increased use.[38] The health information provided to patients on the internet about proton therapy can be inaccurate,[101] especially given its unproven benefits. Moreover, misrepresentation of the benefits of protons is not limited to the USA, as placing the

Table 4 | Selected studies of particle beam therapy for prostate cancer

Study	Type	Treatment (dose)	*n*	Median follow-up time (years)	Actuarial follow-up time (years)	FFBF (%)			RTOG late grade 3–4 toxicity (%)	
						L	I	H	Genitourinary	Gastrointestinal
Protons										
Shipley *et al.*[87] (1995)	Phase III	Arm 1: 3D-CRT + proton therapy (75.6 GyE)	103	5.1	8	77*	77*	77*	NA	NA
Shipley *et al.*[87] (1995)	Phase III	Arm 2: 3D-CRT	99	5.1	8	60*	60*	60*	NA	NA
Yonemoto *et al.*[89] (1997)	Phase I/II	3D-CRT + proton therapy (75 GyE)	104	1.8	2	96	67	63	0	0
Coen *et al.*[86] (2012)	Phase II	3D-CRT + proton therapy (82 GyE)	85	3.1	2.6	NA	NA	NA	6	6
Zietman *et al.*[32] (2010)	RCT	Arm 1: 3D-CRT + proton therapy (70.2 GyE)	197	8.9	10	68	68	NA	2	1
Zietman *et al.*[32] (2010)	RCT	Arm 2: 3D-CRT + proton therapy (79.2 GyE)	196	8.9	10	76	76	NA	2	1
Mendenhall *et al.*[88] (2012)	Prospective	3D-CRT + proton therapy (78–82 GyE)	211	>2	2	100	99	95	2	<1
Neutrons										
Laramore *et al.*[92] (1993)	Phase III	Arm 1: Neutrons + 3D-CRT	55	11	10	NA	NA	70*	11	11
Laramore *et al.*[92] (1993)	Phase III	Arm 2: 3D-CRT	36	11	10	NA	NA	58*	3	3
Forman *et al.*[91] (1997)	Phase I/II	Arm 1: Pure neutrons	87	3	4	92	85	38	11	11
Forman *et al.*[91] (1997)	Phase I/II	Arm 2: 3D-CRT	85	3	4	55	55	55	3	3
Carbon-12										
Tsuji *et al.*[94] (2005)	Phase I/II	^{12}C (54–72 GyE)	201	2.5	5	100	100	80	0	0
Akakura *et al.*[93] (2009)	Phase I/II	^{12}C (66–72 GyE)	69	3.9	5	83	83	83	6	6
Ishikawa *et al.*[95,96] (2006, 2012)	Phase II	^{12}C (57.6–66 GyE)	1,100	3.6	5	90	97	88	1	<1

*Local control achieved. Abbreviations: ^{12}C, carbon-12; 3D-CRT, 3D conformal radiotherapy; FFBF, freedom from biochemical failure; GyE, gray equivalent; H, high-risk prostate cancer; I, intermediate-risk prostate cancer; IMRT, intensity-modulated radiotherapy; L, low-risk prostate cancer; NA, not applicable; RCT, randomized controlled trial; RTOG, Radiation Therapy Oncology Group.

search terms 'prostate cancer proton therapy' into an internet search engine could lead patients from anywhere in the world to inaccurate information about the technology.[101]

The Radiation Oncology Institute identified six co-equal priorities to promote CER in prostate cancer radiotherapy:[109] identify and develop communication strategies to help patients and others better understand radiotherapy, establish indicators for major radiation oncology procedures and evaluate their use in radiation oncology delivery, identify best practices for the management of radiation toxicity and issues in cancer survivorship, conduct prospective CER studies related to radiotherapy that consider clinical benefit, toxicity, quality of life (QOL) and other outcomes, assess the value of radiotherapy and develop a radiation oncology registry. To complement these priorities, equipment manufacturers are being encouraged to develop unique technology identifiers (for example, specific IMRT and IGRT equipment used) for radiotherapeutic devices to facilitate identification in registries or claims data.[110]

Improving outcomes

CER will need to be performed for the patient-specific prognostic factors involved in the use of particular radiotherapy modalities for particular patients. Currently, most studies stage patients according to the NCCN[12] or American Joint Committee on Cancer (AJCC) systems.[111] Although the NCCN staging seems to be superior to the AJCC in terms of stratifying patients into appropriate risk groups, both systems have limitations in their identification and prognostication for men with low-risk and intermediate-risk prostate cancer;[112] moreover, they have limited use for making personalized clinical decisions for a treatment when multiple treatment options exist.[113]

Future staging systems will likely include parameters such as percent of positive biopsy cores and primary Gleason grades,[114] patient-specific characteristics (for example, obesity,[115] changes in bladder and colorectal volumes, pelvic anatomy[116] and prostheses)[117] and cancer-specific biomarkers (for example, Bax, Bcl-2, cyclooxygenase, E-cadherin and Ki67),[112] PET–CT imaging data[118,119] and multiparametric MRI findings.[120,121] These factors and imaging modalities will help identify prostate subvolumes that at the highest risk of cancer dissemination, and could theoretically benefit from further dose escalation using an appropriate modality. Currently, the Focal Lesion Ablative Microboost in Prostate cancer (FLAME)-trial is investigating the effect of an ablative

microboost to the macroscopic tumour for patients with intermediate-risk and high-risk cancer treated with EBRT using multiparametric MRI strategies.[122]

With respect to treatment delivery, the 2D, 3D and 4D IGRT systems discussed in this Review are generally used to improve accuracy and precision of radiotherapy by helping to reduce treatment margins. However, some evidence suggests that extreme reduction of margins negatively affects outcome.[123] Further studies are necessary to find the patients and radiotherapy modalities that would benefit most from each IGRT system.[5] Additionally, no IGRT system is currently perfect in terms of tumour delineation—identification of microscopic disease—because of limitations in spatial resolution and a lack of integration of cancer-specific and patient-specific factors.

Future IMRT and IGRT systems will, therefore, likely integrate novel imaging techniques and patient characteristics to tailor the delivered dose. Novel tools and techniques to be used might include prostate–rectum spacers, which would enable aggressive hypofractionation even with relatively simple IMRT techniques (such as volumetric modulated arc therapy).[124,125] Future IGRT systems will also likely include adaptive dose-deforming radiotherapy algorithms[126,127] and novel fiducial markers.[128] Finally, IMPT seems to be a promising approach that could also target prostate subvolumes.[129]

Predicting and reporting toxicity

Future systems to predict toxicity will likely include single nucleotide polymorphisms (SNPs) of implicated genes, such as *TGFB1*, *FSHR* and *XRCC3* as well as mutations on chromosome 11q14.3, which contains SNPs (rs7120482 and rs17630638) for gene products associated with DNA repair.[130–134] Other factors that will be incorporated into prediction models include relevant patient comorbidities (such as diabetes mellitus and colonic dysmotility),[135,136] previous surgical interventions (such as abdominal surgery and transurethral resection of the prostate),[135] medications (such as ADT)[137] and dose–volume histograms.[138] The inclusion of such factors will help to develop risk profiles that will enable clinicians to tailor radiation doses to particular subvolumes.

With respect to reporting toxicity after treatment, the scales used in the literature are generally not detailed or tailored to individual patients. For example, the RTOG toxicity score does not include the evaluation of anorectal symptoms, including faecal incontinence and urgency of defecation.[139] The exclusion of these symptoms is one reason why the RTOG scale alone was shown to be insufficient in reporting late genitourinary and gastrointestinal toxic effects after IMRT.[9,10] Indeed, the late effects from radiotherapy can occur decades after the initial treatment,[140,141] and are often dependent on the pretreatment symptoms;[142] thus, the use of scales aside from the RTOG scale will be necessary to accurately describe these effects. When compared with studies that measure QOL after treatment with conventional technologies,[15] reported studies of advanced modalities have not integrated patient-reported QOL scales (such as the SF-36, EORTC QLQ-PR25, Expanded Prostate Cancer Index Composite [EPIC] and the International Index of Erectile Function-15 [IIEF-15]).[37,143] Furthermore, reports of toxicity might not be truly representative because studies to date have been conducted in relatively small, undiverse patient populations. Finally, many of the toxicity questionnaires available have not been tested in non-English-speaking communities, and their accuracy must be validated before they are applied globally.[37]

Given the current reporting of gastrointestinal and genitourinary toxicity rates reported using RTOG scales, whether clinicians should aim at reducing them is unclear, as is whether they are high or so low that they are not a clinical priority; comparative data are required. The development of an international registry for toxicities is recommended to address the concerns associated with current toxicity reports.[109] Although large population-based databases exist—such as the Surveillance, Epidemiology, and End-Results registry—the need for a radiation-oncology-specific database is pressing. Such a database might include multiple QOL questionnaires and patient-specific factors (including SNPs, comorbidities and drug use).

Effectiveness

Most healthcare recommendations around the world are based on studies designed to evaluate efficacy, which measures whether one novel intervention has an impact on outcomes under ideal conditions. The arms of studies assessing efficacy include the treatment under consideration versus control or observation. The advanced radiotherapy modalities discussed in this Review are known to be efficacious—they improve outcomes. However, CER also focuses on treatment effectiveness—whether the intervention has an effect under real-world conditions and how efficacious the treatment is compared with other modalities.[144] Effectiveness studies of HDR-BT, SBRT and proton beam therapy will be performed in the future.

Although the initial reports of outcomes and toxicity of HDR-BT, SBRT and proton beam therapy have been encouraging, a number of limitations are apparent when comparing these with studies of established conventional modalities.[14] Median follow-up times of the advanced radiotherapy modalities are generally considerably shorter than those of established therapies (typically <4 years versus >8 years). Secondly, many more patients have been treated with established modalities than with any of the newer technologies. Additionally, outcomes in men with intermediate-risk and high-risk prostate cancer have been limited, only reported in a few studies of SBRT[75,76,79] and particle therapies.[87–89,91,92,94–96] Finally, many of the studies with newer technologies (particularly SBRT and proton beams) are single-institution experiences, whereas those of conventional therapies are prospective multicentre randomized trials.

Designing randomized controlled trials that compare any of the advanced modalities with other treatment options available for prostate cancer would be difficult. Long follow-up times (>10 years) would be necessary because the prostate cancer-specific survival at 5 years is typically >97%, >90% and >85% for men with low-risk, intermediate-risk and high-risk localized disease.[145,146]

Moreover, multiple comparative treatment options could be selected for patients with low-risk and intermediate-risk disease, the varying efficacies between the risk groups.[14] Additionally, active surveillance could be a comparator arm for low-risk patients because of the relatively high overall survival and low prostate cancer-specific survival. Finally, for certain advanced modalities, namely proton therapy and SBRT, too few centres in the world are equipped to treat patients, let alone accrue patients as quickly as other modalities; the construction of new centres is prohibitively costly for many hospitals.

Although a randomized controlled trial comparing IMRT to proton therapy would be a good investment, the cost of such a trial would range from $5–15 million, likely over about 5 years.[110] Additionally, the conclusions that clinicians attempt to draw from RTOG clinical trials that include these advanced technologies might be limited. RTOG trials from previous decades included specific constraints regarding modalities that could or could not be tested (such as conventionally fractionated EBRT and LDR-BT). Many of the current RTOG trials are stratified by technology type to determine whether they affect outcomes, even though most, if not all, do not yet have equivalent efficacy or effectiveness when compared with conventional therapies. That is, if the theoretical benefits of any of the new technologies do not transfer to the clinical setting, the outcomes of the trials will be hypothesis-generating, but inconclusive.

Efficiency

CER also focuses on efficiency: whether an intervention is worth the resources it consumes,[144] which is determined using analyses of the economic impact of interventions with cost–effect and cost–benefit analyses.[147] Calculation models have shown that wage costs outweigh the cost of instruments in radiotherapy because of the labour-intensive nature of planning and delivery.[148–150] For conventionally fractionated EBRT, staffing radiotherapy facilities are estimated to be 50% of the total treatment cost.[151] Moreover, although treatment planning is more complex with all of the advanced technologies (compared with 3D-CRT), planning is only done at the beginning of therapy, whereas cost increases with the delivery of each fraction.[152] Thus, changing to an SBRT schedule might decrease the number of work-hours and overall cost of treating each patient.[72]

On the basis of Medicare reimbursements, per-patient costs of LDR-BT, HDR-BT with four fractions and conventionally fractionated EBRT (with IMRT) are estimated at $9,938, $17,514 and $29,356, respectively.[153] Thus, some argue that LDR-BT and HDR-BT not only provide excellent clinical outcomes, but are cost effective. Treatment of patients with proton therapy seems to be more expensive than treatment with any of the other modalities, at >$50,000–60,000.[97,103,104] Given the many factors involved in radiotherapy delivery—including costs of constructing a facility, the IGRT and IMRT systems necessary, number of fractions needed, number of patients treated at each facility, patient outcomes, toxic effects experienced, patient time away from work and patient satisfaction—comparing the efficiency of the different advance technologies is currently difficult.

Conclusions

For men with localized prostate cancer, the use of novel advanced radiotherapy modalities—HDR-BT, SBRT and proton beam therapy—is infrequently mentioned in articles comparing outcomes and toxicities of patients treated with conventional radiation therapies (conventionally fractionated EBRT and LDR-BT). IGRT and IMRT, which have been important in the development of these novel modalities, and radiobiological models, which support high dose per fraction radiotherapy, have been critical for the introduction and evolution of these three novel modalities. On the basis of published evidence, conventionally fractionated EBRT with IMRT is the standard of care over 3D-CRT, HDR-BT boost is an acceptable treatment option for selected patients with intermediate-risk and high-risk prostate cancer and SBRT and proton therapy should not be used for patients (regardless of disease risk group) outside the setting of a clinical trial. CER will further help provide a framework for evaluating advanced radiotherapeutic technologies by comparing the benefits and harms to optimize the risk:benefit ratio and improve cost-effectiveness.

Review criteria

The MEDLINE and PubMed databases were searched for original articles focusing on prostate cancer radiotherapy published between 1970 and 2012. The search terms used were “prostate cancer” and “radiation therapy” combined with any of: “high dose rate brachytherapy”, “stereotactic body radiation therapy”, “carbon”, “neutron”, or “proton”. All papers identified were English-language full text papers. The reference lists of identified articles were searched for further papers.

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Author contributions

N. G. Zaorsky researched the data for the article and wrote the manuscript. All authors discussed the article's content and edited the manuscript before submission.