



Practical considerations for prostate hypofractionation in the developing world

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Abstract | External beam radiotherapy is an effective curative treatment option for localized prostate cancer, the most common cancer in men worldwide. However, conventionally fractionated courses of curative external beam radiotherapy are usually 8–9 weeks long, resulting in a substantial burden to patients and the health-care system. This problem is exacerbated in low-income and middle-income countries where health-care resources might be scarce and patient funds limited. Trials have shown a clinical equipoise between hypofractionated schedules of radiotherapy and conventionally fractionated treatments, with the advantage of drastically shortening treatment durations with the use of hypofractionation. The hypofractionated schedules are supported by modern consensus guidelines for implementation in clinical practice. Furthermore, several economic evaluations have shown improved cost effectiveness of hypofractionated therapy compared with conventional schedules. However, these techniques demand complex infrastructure and advanced personnel training. Thus, a number of practical considerations must be borne in mind when implementing hypofractionation in low-income and middle-income countries, but the potential gain in the treatment of this patient population is substantial.

Cancer incidence continues to increase and malignancy now represents the second most common cause of death and disability-adjusted life years worldwide after cardiovascular disease¹. Prostate carcinoma is the third most prevalent type of cancer worldwide, with over 1,400,000 cases in 2020 and is the most common cancer in men; ~375,000 deaths from prostate were expected in the same year worldwide². Prostate cancer incidence is rising owing to increased prostate-specific antigen (PSA) screening, longer life expectancy and growing awareness in men's health. Although the incidence of prostate cancer remains highest in developed countries, the mortality rate is disproportionately higher in low-income and middle-income countries (LMICs). A 2016 analysis of global prostate cancer burden reported age-standardized incidence rates of 68 cases and 14.5 cases per 100,000 in developed and developing countries, respectively, and the respective mortality rates were 10 (15%) and 6.6 (46%) per 100,000 (REF.³).

Only a minority (~5%) of patients present with metastatic disease at the time of diagnosis⁴. Most patients have localized disease that is amenable to curative-intent treatment, with various management alternatives available, including surgery, external beam radiotherapy

(EBRT) and brachytherapy. Radiation treatment and surgery have been shown to have equivalent long-term oncological outcomes, with differences only in the rates and types of associated adverse effects⁵. An analysis of patient-reported outcomes from the PROTECT trial (NCT02044172) — the largest and most influential randomized evidence comparing patients with localized prostate cancer to active surveillance, EBRT and radical prostatectomy — revealed higher rates of sexual dysfunction and urinary incontinence in patients who underwent prostatectomy, whereas EBRT was associated with a higher risk of gastrointestinal (GI) toxicity⁶. Notably, although the trial outcomes showed equivalence in oncological end points, the majority of patients were low risk, with >75% of patients having Gleason 6 disease and 90% having a PSA levels of <10 ng/ml (REF.⁷).

Traditionally, curative-intent EBRT has been delivered using conventional fractionation schedules, treating patients with 1.8–2.0 Gy per day. Initial studies have established that total doses of radiotherapy of 76–78 Gy, compared with lower doses of 68–70 Gy, improve disease control rates by approximately 10–15% at 5 years^{8–10}. However, such treatment, albeit effective, entails a treatment course that spans over 7–8 weeks' duration.

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Key points

- The global burden of prostate cancer is increasing and prostate cancer is becoming a major source of health-care burden in low-income and middle-income countries (LMICs).
- Radiotherapy is an essential treatment modality in the management of prostate cancer. However, radiotherapy resources are lacking in LMICs, resulting in excess morbidity and mortality.
- Hypofractionated radiotherapy schedules offer an opportunity to maintain excellent treatment outcomes while shortening curative radiotherapy courses. This approach expands the treatment capacity and could improve crucial access in communities with limited radiotherapy resources.
- Initial investments are required for technological upgrades, such as intensity-modulated radiotherapy and image-guided radiotherapy, as well as in specialized training in order to optimally provide hypofractionated treatment. Discussion amongst government agencies and device manufacturers is essential to lower these costs.
- Personnel training and access to external consultation are critical resources for developing radiotherapy centres. Information and communication technologies enable remote guidance between developing and developed radiotherapy centres.
- In the long term, hypofractionation programmes result in long-term cost savings and simultaneously expand patient access to a curative modality in the management of prostate cancer.

Alpha/beta ratio

The ratio of linear and quadratic components that make up the model of cancer cell killing in response to radiotherapy; a measure of intrinsic sensitivity of a cell to radiation-induced death.

The time and financial costs to both the patient and the treatment centre can be substantial. In limited-resource settings, alternative treatment options are necessary and hypofractionation presents that opportunity.

Over the past three decades, technological advancements in radiotherapy planning and delivery have enabled increased precision and accuracy for the treatment of prostate cancer with the advent of intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) technologies¹¹. The former enables fine dose shaping of the target while sparing nearby organs, whereas the latter ensures accuracy in patient setup for each radiation fraction. As such, several phase III randomized trials have investigated and established the clinical efficacy of hypofractionated radiotherapy schedules^{12–20}. Hypofractionated radiotherapy schedules provide a larger dose per fraction than the conventional schedules that deliver 1.8–2 Gy. In addition to shortened treatment durations, hypofractionation could present an additional biological benefit in that prostate cancers are thought to have a higher intrinsic sensitivity to larger fraction sizes owing to a posited lower alpha/beta ratio²¹.

The American Society for Radiation Oncology (ASTRO), American Society of Clinical Oncology (ASCO) and American Urological Association (AUA) recognize

that moderate hypofractionation is a compelling option in men with prostate cancer across all risk groups receiving EBRT to the prostate alone as endorsed in their 2018 joint guideline²². In moderate hypofractionation, the per fraction dose ranges between 2.4 and 3.4 Gy; the most commonly used regimen is 60 Gy in 20 fractions over 4 weeks. The joint guideline also makes a conditional recommendation for the use of ultra-hypofractionation in low-risk and intermediate-risk prostate cancer. The guideline defines ultra-hypofractionation as EBRT with a per fraction dose of ≥ 5 Gy. Usual regimens include 36.5 Gy in 5 fractions, 42.7 Gy in 7 fractions or 35 Gy in 5 fractions²². Furthermore, with the use of IMRT technology, ultra-hypofractionated radiotherapy can be delivered with increased precision and a sharp dose fall-off to surrounding normal tissues in a technique referred to as stereotactic body radiotherapy (SBRT).

This Review will acknowledge and contextualize the advantages that these shorter treatment courses could have for health-care systems, patients and caregivers, particularly in LMICs. We describe the evidence supporting the use of these treatment schemes, their technological requisites and the economic impacts of hypofractionation as they pertain to developing nations.

Framing the issue: global necessity and disparities

Radiotherapy is extensively used in the management of prostate cancer²³. The optimal radiotherapy utilization rate in patients with prostate cancer — that is, the ideal number of patients who should receive it within the clinical context — has been estimated at ~60%^{24,25}. This value is corroborated by the use of population-based data to verify estimates of need models in which 61% of prostate cancer patients were estimated to require radiation within 5 years of diagnosis²⁶.

Despite the importance of radiotherapy in cancer treatment, radiotherapy centres are in short supply worldwide and >90% of patients in LMICs do not have access to this treatment modality²⁷. A 2013 report by the International Atomic Energy Agency reported that only 23 of 52 African countries have access to EBRT²⁸. A subsequent 2020 study of 84 LMICs using GLOBOCAN data revealed that only 4 (5%) had the requisite number of radiotherapy units and that almost 40% did not have any facilities present at all. The study projected that these figures will continue to worsen and constitutes a “silent crisis”²⁹. In addition to these data demonstrating the paucity of radiotherapy availability in LMICs, a 2014 report by the Global Task Force on Cancer Care and Control highlighted that between one-third and half of global cancer deaths are avoidable and that 80% of these are in LMICs, where access to radiotherapy is one of the largest gaps in cancer care³⁰.

In Brazil, an upper-middle-income country, close to 110,000 patients (about 20% of cancer diagnoses) requiring radiotherapy were estimated to miss out on receiving this treatment. As a result, >5,000 deaths were attributable to the lack of adequate treatment for the five most common cancers, namely prostate, breast, colorectal, lung and cervical cancers³¹. Part of the issue is antiquated technology; a 2019 Brazilian federal census showed that 34% of the radiotherapy machines in Brazil

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were obsolete, with this proportion projected to grow to 51% in 2022 if replacements are not acquired³².

Even in high-income countries disparities exist in access to radiotherapy. A study from Sweden, a high-income country, found that patients with a low income and who were unmarried had a higher likelihood of not receiving standard-of-care radiotherapy management for their cancer³³. Often, the reason for this discrepancy is geographical, with patients living in rural areas being disproportionately affected³⁴. The use of shorter treatment courses with hypofractionation can mitigate this latter issue by reducing travel expenses and increasing patient convenience^{35,36}.

Thus, radiotherapy access is a global concern. However, the effects of this lack of access are most pronounced in the developing world, where the greatest disparity exists. The 2015 report by the Lancet Oncology Commission called for an action plan that aimed to increase radiotherapy treatment capacity by 25% in 2025 compared with capacity in 2015 (REF.³⁷). Progress on these goals involving capacity-building in radiotherapy access is being actively investigated by the senior author of this Review and is pending publication. Hypofractionation offers the opportunity to increase treatment capacity for a single radiotherapy machine by simply reducing the number of treatment sessions required per patient, thereby expanding machine capacity for a disease that is becoming more and more common as the developing world advances.

Clinical evidence

A number of clinical trials have evaluated the benefits and outcomes associated with moderate and ultra-hypofractionation in men with prostate cancer as well as the role of concurrent androgen deprivation therapy (ADT).

Evidence supporting moderate hypofractionation.

The joint guideline recognizes that moderate hypofractionation should be offered to men with low-risk, intermediate-risk and high-risk prostate cancer; common fractionation schedules typically administer 60–72 Gy over 4–6 weeks^{12–14,16–18,38}. The bulk of current evidence supports equivalent results with the use of 60 Gy in 20 fractions over 4 weeks to the prostate with or without the inclusion of seminal vesicles and omission of pelvic lymph nodes compared with conventional fractionation²². This schedule was evaluated across patients with predominantly low-risk and intermediate-risk disease in two phase III trials in the presence or absence of ADT^{16,18}.

Seven prospective randomized control trials (RCTs), including close to 6,500 patients in total, have been performed from 2013 to 2019, and demonstrate that moderate hypofractionation renders comparable disease control rates to conventional fractionated regimens^{12–14,16–18,38}. The largest of these include the CHHiP and PROFIT trials^{16,18}. The former trial enrolled 3,200 patients of all risk groups, although >70% of patients fell into the intermediate risk category. Patients were randomized to one of three arms: the conventional arm of 74 Gy in 34 fractions or one of two hypofractionation arms,

of either 60 Gy in 20 fractions or 57 Gy in 19 fractions. After a median follow-up of approximately 5 years, 60 Gy in 20 fractions were found to be non-inferior to 74 Gy in 34 fractions in terms of clinical or biochemical failure, with 90.6% and 88.3% of patients being failure free in the hypofractionated and conventional arms, respectively ($p=0.0018$). Similarly, long-term toxicity did not differ between the arms¹⁶. The PROFIT trial enrolled 1,200 patients with intermediate-risk disease and randomized them to conventional 78 Gy in 39 fractions versus hypofractionated 60 Gy in 20 fractions. At 5 years, the biochemical recurrence-free survival (BCFS) was 85% in both arms. Grade 3 or greater late toxicity did not differ significantly between the two arms¹⁸. (TABLE 1).

Overall, the data from these RCTs suggest that the efficacy of moderate hypofractionation is not influenced by patient comorbidity, age, anatomy or urinary function. Late GI and genitourinary (GU) toxic effects are comparable between the two fractionation schemes, although RTOG 0415 and HYPRO did report a higher incidence of late toxicity with hypofractionation^{14,15}. Acute GU toxicity was also similar in both groups; however, moderate hypofractionation might be correlated with a higher risk of acute GI toxicity. In the CHHiP trial, grade 2 or greater acute GI toxicity was observed in 38% of patients who received 60 Gy in 20 fractions compared to 25% of patients in the conventional arm ($p<0.0001$)¹⁶. Similarly, Aluwini et al. observed a grade 2 or greater acute GI toxicity incidence of 42% versus 31.2% in the hypofractionated and conventional arms, respectively ($p=0.0015$)³⁹. The increase in toxicity observed in the hypofractionated arms of these studies could be explained in part by the higher biological equivalent dose (BED) used. BED is a function of total dose and is a proportional dose per fraction. It has been proposed that BEDs of >180 Gy are associated with a greater risk of toxicity⁴⁰. Some patient characteristics (prostate volume, age, and baseline GI and/or GU symptoms) are correlated with an increased risk of toxicity despite conventional or hypofractionation schedules²². Similarly, a Cochrane meta-analysis of 10 RCTs with a total of 8,278 patients showed no difference in overall survival (HR 0.94, 95% CI 0.83–1.07) and equivalent prostate cancer-specific survival (HR 1.00, 95% CI 0.72–1.39) between hypofractionation and conventional fractionation. In this Cochrane review, only acute GI toxicity was found to be higher in moderate hypofractionation compared with conventional schedules (RR 1.45, 95% CI 1.19–1.75)⁴¹.

Evidence for ultra-hypofractionation. The 2018 joint guideline presents a conditional recommendation for ultra-hypofractionation as an alternative to conventional EBRT in patients with low-risk and intermediate-risk disease²². When the guideline was released, these recommendations were conditional on new data becoming available from ongoing randomized trials. The National Comprehensive Cancer Network (NCCN) lists SBRT as an appropriate treatment option for patients with localized prostate cancer in all risk groups⁴². Two key phase III trials, both of which were published after the joint guideline, support ultra-hypofractionation^{19,20}

Table 1 | Key randomized trials comparing radiotherapy fractionation strategies

Study	Publication year	Number of patients	Eligibility criteria	Study design	Oncological outcome	Toxic effects
Trials comparing conventional and moderate hypofractionation						
Pollack et al. ¹²	2013	303	Any risk	76 Gy/38 vs 70.2 Gy/26 fractions; all patients received ADT (24 months if high risk, 4 months otherwise); superiority design	5-year BCDF was 21.4% in the 76 Gy arm and 23.3% in the 70.2 Gy arm ($p=0.745$); no significant difference between arms	No significant difference in late toxicity
Hoffman et al. ¹³	2014	222	Any risk	75.6 Gy/42 vs 72 Gy/30 fractions; some patients received ADT (1/4 of patients); superiority design	Pending	No significant difference in grade 2 or greater late GU or GI toxicity
RTOG 0415 (REF. ¹⁴)	2016	1,115	Low risk	73.8 Gy/41 vs 70 Gy/28 fractions; no ADT; non-inferiority design	5-year DFS 85.3% in the 73.8 Gy arm and 86.3% in the 70 Gy arm (HR 0.85, 95% CI 0.64–1.14); hypofractionation was non-inferior	Worse grade 2 and 3 late GI and GU toxicities in the hypofractionation arm
HYPRO ³⁸	2016	820	Intermediate and high risk	78 Gy/39 vs 64.6 Gy/19 fractions; ADT as per institutional protocol (2/3 of patients); superiority design	5-year RFS was 80.5% in the 64.6 Gy arm and 77.1% in the 78 Gy arm ($p=0.36$); no significant difference between arms	Worse grade ≥ 2 acute GI toxicity in the hypofractionated arm ³⁹ ; could not prove non-inferior late toxicity in hypofractionation arm ¹⁵
CHHiP ¹⁶	2016	3,216	Any risk	74 Gy/37 vs 60 Gy/20 vs 57 Gy/19 fractions; all patients had 3–6 months of ADT (except low risk); non-inferiority design	5-year BCFS was 88.3%, 90.6% and 85.9% in the 74, 60 and 57 Gy arms, respectively; 60 Gy/20 was non-inferior to 74 Gy/37 fractions (HR 0.84, 90% CI 0.68–1.03)	No significant difference in cumulative incidence of side effects 5-years post treatment using clinician and PRO measures
PROFIT ¹⁸	2017	1,206	Intermediate risk	78 Gy/39 vs 60 Gy/20 fractions; no ADT; non-inferiority design	5-year BCFS was 85% in both arms (HR 0.96, 90% CI 0.77–1.2); hypofractionation was non-inferior	No significant difference in grade 3 or greater late GI or GU toxicity
Arcangeli et al. ^{17a}	2017	168	High risk	80 Gy/40 vs 62 Gy/20 fractions; all patients had 9 months of ADT; superiority design	10-year BCFS was 72% in 62 Gy arm vs 65% in 80 Gy arm ($p=0.148$); no significant difference between arms	No significant difference in clinician-assessed grade 2 or greater late GI or GU toxicity ^a
Trials comparing moderate conventional, hypofractionated and stereotactic body radiotherapy						
PACE-B ¹⁹	2019	874	Low and intermediate risk	78 Gy/39 vs 62 Gy/20 vs 36.25 Gy/5 fractions; no ADT; non-inferiority design	Pending	No difference in acute GI or GU toxicity
HYPO-RT-PC ²⁰	2019	1,200	Intermediate and high risk	78 Gy/39 vs 42.7 Gy/7 fractions; no ADT; non-inferiority design	5-year RFS was 84% in both arms (HR 1.002, 95% CI 0.758–1.325); SBRT was non-inferior	Worse late GU toxicity in SBRT arm at 1 year using clinician and PRO measures; significantly higher acute GI and GU toxicity in the SBRT arm using PRO measures but not observed in clinician-reported outcomes

ADT, androgen deprivation therapy; BCDF, biochemical and/or clinical disease failure; BCFS, biochemical recurrence-free survival; DFS, disease-free survival; PRO, patient-reported outcomes; GI, gastrointestinal; GU, genitourinary; RFS, relapse-free survival; SBRT, stereotactic body radiotherapy. ^aPrimary outcome for this trial was assessing late toxicity.

(TABLE 1). HYPO-RT-PC randomized 1,200 patients with intermediate-risk and high-risk disease to 78 Gy in 39 fractions versus 42.7 Gy in 7 fractions²⁰. After 5 years, failure-free survival in patients who received SBRT was non-inferior to conventional fractionation, at

85% in both arms ($p=0.99$). However, patients in the ultra-hypofractionation arm experienced significantly more grade ≥ 2 GU and GI toxic effects after radiotherapy up to 3 months post treatment than patients in the conventional therapy arm. However, these differences

dissipated with longer follow-up duration, except for GU toxicity alone, which, at 1 year, was significantly higher for ultra-hypofractionation at 6% compared with 2% in the conventional therapy arm ($p=0.004$). PACE-B was a non-inferiority trial of 874 patients with low-risk and intermediate-risk prostate cancer who were randomized to 78 Gy in 39 fractions, 62 Gy in 20 fractions or 36.25 Gy in 5 fractions¹⁹. No differences were observed in grade 2 or worse acute GI toxicity between the conventional or moderate hypofractionation versus the SBRT arms, with an incidence of 12% and 10%, respectively ($p=0.38$). Similarly, grade ≥ 2 acute GU toxic effects between these same groups was at 27% versus 23% ($p=0.16$). Oncological outcomes are still eagerly awaited. The promising early toxicity data from PACE-B compared with HYPO-RT-PC suggest that the lower BED in this trial might be preferable. Additionally, all patients in PACE-B were treated with SBRT rather than non-intensity-modulated techniques, whereas this proportion was only 20% in HYPO-RT-PC.

A key aspect to note in these randomized trials is that the majority of patients enrolled had low-risk or intermediate-risk disease. Only 11% of patients in HYPO-RT-PC (NCT03274687) had high-risk disease as defined by T-stage or Gleason grade, suggesting that extrapolation of ultra-hypofractionation to this patient population should be done with caution²⁰. Furthermore, the majority (95%) of patients in the PACE-B (NCT01584258) trial had prostate volumes of <80 cc (REF.¹⁹). A 2015 dosimetric analysis of prostate volumes in prostate cancer patients receiving SBRT reported that patients with a V100 (volume receiving 100% of the prescription dose) of >120 cc had the greatest decline in urinary quality of life (QoL)⁴³. Prostate size was not reported in HYPO-RT-PC and, therefore, this detail could further explain the differences in acute toxicities between the two trials. Nevertheless, the results of these trials support the non-inferiority of disease control of ultra-hypofractionation in comparison to moderate hypofractionation and conventional schedules with similar toxicity profiles^{19,20}.

A 2019 systematic review and meta-analysis assessed $>6,000$ patients treated with SBRT in 38 prospective trials with a median follow-up period of 39 months⁴⁴. In this meta-analysis, the majority of patients had intermediate-risk disease ($n=2,901$), with 78% of included studies containing some proportion of this patient population. Of the 38 trials in the meta-analysis, 92% included patients with low-risk disease and only 38% included patients with high-risk disease. Using data from 2,343 patients in 14 studies, the meta-analysis calculated the overall 5-year BCFS at 95.3% (95% CI 91.3–97.5; $p<0.001$); in patients with intermediate-risk disease, the 5-year BCRFS was slightly lower, at 92.1% (95% CI 89.2–94.3), whereas BCRFS was 96.7% (95% CI 95.2–97.8) in patients with low-risk disease. Trials including patients with high-risk prostate cancer rarely described the BCRFS results and, therefore, quantitative synthesis was not performed in this patient subset. The estimated incidences of late grade ≥ 3 GI and GU events were 1.1% (95% CI 0.6–2.0) and 2.0% (95% CI 1.4–2.8), respectively. QoL outcomes measured

using the Expanded Prostate Cancer Index Composite (EPIC-26) questionnaire were reported in 25 studies and 3,293 patients. Both GU and GI EPIC-26 scores returned to pre-radiotherapy baseline 2 years after treatment and remained non-significantly different at 5 years compared with the 2-year scores ($p=0.5$ and $p=0.8$ for GU and GI, respectively). This meta-analysis provides evidence that SBRT for localized prostate cancer is associated with excellent disease control, minimal toxicity and negligible effects on QoL⁴⁴. Notably, these data largely pertain to patients with low-risk and intermediate-risk disease and, therefore, cannot routinely be applied to patients with high-risk disease.

Role of ADT in hypofractionation. ADT plays an essential role in the management of high-risk and unfavourable intermediate-risk (UIR) prostate cancers treated with radiotherapy. Several trials have established the benefit of the addition of 18–36 months of ADT in patients with high-risk disease and of 4–6 months of ADT in patients with intermediate-risk disease treated with conventionally fractionated radiotherapy schedules^{45–52}. The AUA/ASTRO/Society of Urologic Oncology (SUO) Guideline on the management of clinically localized prostate cancer recommends the use of concurrent ADT in these risk groups in the setting of definitive radiotherapy⁵³.

However, the benefit of ADT is not as well defined in the setting of hypofractionation given that no comparative, randomized trials have directly evaluated this question. The use of ADT was heterogeneous in the moderate hypofractionation trials discussed in this current Review and ranged from none of the patients in the study to the entire cohort, making the contribution of ADT difficult to determine. Nevertheless, the oncological outcomes between the hypofractionated arms of these trials do not seem to drastically differ^{12,14,16–18,38} (TABLE 1).

Interestingly, none of the patients in the PACE-B or HYPO-RT-PC ultra-hypofractionation trials received ADT, although PACE-B excluded patients with high-risk disease and only a minority of patients had high-risk disease in HYPO-RT-PC^{19,20}.

Thus, ADT was not strongly indicated for the majority of patients enrolled in these trials.

However, several studies in the past few years have investigated the role of ADT in the setting of ultra-hypofractionation for patients with high-risk and UIR disease. A National Cancer Database (NCDB) analysis compared 558 men who received SBRT with 40,797 men who received moderate hypofractionation or conventionally fractionated radiotherapy for the treatment of high-risk or UIR prostate cancer; all patients received concurrent ADT. The study revealed no difference in survival between the two cohorts at 6 years after treatment⁵⁴. A prospective phase II trial of 154 men with UIR or high-risk prostate cancer treated with SBRT plus 6 months or 24 months of ADT (for UIR and high-risk disease, respectively) reported a favourable 5-year BCFS of 97% and reasonable rates of late grade ≥ 2 GI and GU toxicities at 7% and 18%, respectively⁵⁵. No cases of grade 4+ toxicity were reported, which is consistent with the safety data from another phase I/II prospective study

Cone-beam CT

(CBCT). A medical imaging technique utilizing divergent X-ray beams to perform CT. Often used for onboard image-guided radiotherapy.

Co-registered

Within treatment planning systems, the fusion or overlay of two separate images, often of different modalities (for example, MRI and CT) to aid treatment planning.

Soft-tissue matching

During image-guided radiotherapy, matching is performed before each treatment fraction to ensure treatment accuracy. In prostate radiotherapy using CBCT, the soft tissue interface between the rectum and prostate (as opposed to bony landmarks) are used for set-up verification.

evaluating 35 Gy in 5 fractions with concurrent ADT in patients with high-risk disease⁵⁶. SHARP, a multicentre, prospective consortium⁵⁷, reported the outcomes of 344 patients with high-risk prostate cancer treated with SBRT, of whom 72% received concurrent ADT. At 4 years after treatment, BCFS and distant metastasis-free survival were 82% and 89%, respectively, suggesting reasonable oncological control. Furthermore, late grade 3+ toxicities were low, at <3%⁵⁷. Together, these results support the role of SBRT with the addition of ADT in patients with high-risk disease, although further randomized evaluation is certainly warranted.

Summary of evidence

The NCCN⁴² and 2018 joint²² guidelines suggest moderate hypofractionated radiotherapy as a standard of care in patients with all risk categories of prostate cancer. These guidelines also recognize that, with appropriate expertise and technology, ultra-hypofractionation is a reasonable option for patients with localized disease in patients with low-risk or intermediate-risk disease^{22,42}. In light of the COVID-19 pandemic, SBRT is being encouraged as the schedule of choice for eligible patients in order to minimize hospital visits and, therefore, infection exposure⁵⁸.

Given that improvement in overall survival has never been observed with any treatment scheme, whether it be hypofractionation, SBRT or conventional dose escalation, other factors need to be considered when determining the optimal management option for patients. Consequently, patient convenience and cost-effectiveness are of utmost importance when determining the best therapy option for patients with localized disease.

Technical considerations

As radiotherapy precision evolves, so too do the technical requirements to necessitate its delivery. At a minimum, modern prostate radiotherapy involves CT-based simulation to guide subsequent treatment using megavoltage linear accelerators (LINACs). Additional upgrades are necessary for advanced methods such as intensity modulation and image-guided treatment delivery.

Treatment simulation. Standard treatment simulation for patients with prostate cancer who will undergo either moderate hypofractionation or SBRT uses CT in the first instance. CT simulation requires several considerations to ensure simulation quality and reproducibility of treatment set-up, particularly relating to intra-patient variability in rectal and bladder filling and prioritizing dose reduction to these structures as critical organs at risk (OARs). To minimize rectal filling discrepancies, patients are instructed to empty their bowels before simulation, using enemas, suppositories and probiotics, although no single rectal management method has been deemed optimal⁵⁹.

Both retrospective and prospective series have found significant associations between rectal distension and decreased disease control, although this association can be reduced by daily cone-beam CT (CBCT) imaging^{60,61}. Furthermore, in addition to bowel preparation, patients are commonly asked to empty their

bladder and to drink a standardized quantity of fluids before they undergo simulation to maintain consistent pelvic anatomy between treatments and to reduce the amount of bladder and bowel inside the treatment field, decreasing the likelihood and severity of toxic effects. A treatment-planning study investigating the effect of bladder filling on radiation dose showed that the median effective dose received by the bladder differed by 20 Gy between a full and empty bladder scan for a radical prostate plan⁶².

In centres with the capacity to also perform MRI simulation, data support an overall reduction of contoured prostate volume of approximately 26% when comparing combined CT–MRI co-registered treatment planning for target delineation with CT simulation alone and is possibly associated with reductions in acute GU toxicity⁶³. Evidence also suggests that combined CT–MRI can better delineate and spare dosing to erectile tissue, although whether this dose reduction translates into decreased erectile toxicity has yet to be established⁶⁴. POTEN-C (NCT03525262) is a phase II RCT currently accruing to evaluate the outcomes of neurovascular bundle sparing in prostate SBRT. The trial is expected to complete accrual in June 2024, with a target of 120 patients randomized 1:1 to neurovascular-sparing and non-sparing arms⁶⁵.

However, much of the evidence to date for hypofractionation has not relied exclusively on MRI guidance for treatment planning; for example, in HYPO-RT-PC and PACE-B, MR-fusion during the simulation process was highly recommended but not mandated. We would recommend the routine addition of MR-fusion if available for ultra-hypofractionation treatment planning; however, it is not essential if not available given that much of the evidence base was developed without it.

Precise target localization before the delivery of each fraction is critical in SBRT owing to the high radiotherapy doses used. For prostate SBRT, transrectal ultrasonography-guided insertion of fiducial seed markers is often performed before simulation to improve target localization. Typically, patients are simulated 7 days after marker insertion to allow for possible seed migration, although some evidence suggests that, in the absence of oedema, seed positions do not vary substantially between insertion and simulation^{66–68}. Fiducial marker implantation facilitates the targeting of radiotherapy and increases the accuracy of CBCT matching by up to 91% in the lateral direction and 64% in both the anterior–posterior and superior–inferior directions, respectively, compared with soft-tissue matching alone^{69,70}. Fiducial markers are typically created from a radio-opaque metal such as gold and 3–4 fiducials are usually inserted inside the prostate at different levels of the gland in non-coplanar positions⁷¹. Insertion is performed as a 5–10-minute outpatient procedure under local anaesthesia and is commonly well tolerated. Severe adverse events are uncommon: a small number of patients experience urinary urgency (16%), haematuria (13%) or haematospermia (10%). In rare instances, systemic infection could occur in about 3% of patients⁷². Although recommended, fiducial placement is not mandatory if daily CBCT is available and implemented^{73,74}.

The use of rectal hydrogel spacers (SPACEOAR) can be considered to decrease rectal dose and potential toxicity in patients receiving SBRT. A dosimetric analysis determined that the addition of rectal spacers resulted in a significant decrease of the volume of rectum receiving 28 Gy or more in patients treated with 35 Gy in 5 fractions as per linear correlation analysis ($r = 0.626$; $p = 0.04$)⁷⁵. Similarly, in a phase I trial of 551 patients treated with SBRT, the use of hydrogel spacers was associated with significantly lower risk of grade 2+ late GI (HR 0.24; $p = 0.01$) and GU (HR 0.37; $p < 0.001$) toxicities compared with no spacer insertion⁷⁶. Economic evaluations have suggested long-term cost effectiveness with the use of SPACEOAR, particularly in the setting of SBRT^{77,78}; however, the initial cost of this patented procedure, which is on average US\$ 2,500 per patient, as well as the technical expertise required for the injection might prove to be prohibitive in LMICs⁷⁹. Furthermore, scepticism exists regarding the efficacy of SPACEOAR given that the initial randomized evidence supporting its approval did not meet the primary end point of acute GI toxicity improvement in the initial analysis^{80,81}. Furthermore, neither the PACE-B nor the HYPO-RT-PC phase III trials of prostate ultra-hypofractionation mandated the use of hydrogel spacer injections^{19,20}.

Treatment planning. The adaptation of standardized procedures for OAR and target delineation, such as those recommended by the European Society for Radiotherapy and Oncology guidelines⁸², is useful for both SBRT and moderate hypofractionation in order to ensure that treatment is in accordance with tried and tested protocols. For instance, the PROFIT (NCT00304759) trial¹⁸ and CHHiP (ISRCTN97182923)/RTOG 0415 (NCT00331773) studies^{14,16} contour the rectum using different methods: rectal wall versus hollow structure, respectively. As such, that clinicians follow radiotherapy planning protocols carefully is critical in order to provide safe and effective treatment for patients. Defining a consistent method for planning and evaluation is paramount for each radiotherapy department as the OAR delineation method of choice must be correlated with its corresponding dose–volume constraints.

The clinical target volume includes the entire prostate and, in patients with intermediate-risk and high-risk disease, also incorporates the proximal seminal vesicles as defined on CT or MRI fusion. A planning target volume (PTV) is created as a 5–10 mm expansion on the clinical target volume for hypofractionation and can be 3–7 mm for SBRT; this margin varies based on institutional type, frequency of IGRT, and bladder and bowel preparation policies⁸³.

The 2018 joint guideline provides recommendations for normal tissue constraints for moderate hypofractionation or SBRT based on several published reference trials^{12–14,16–18,22,84–86}. Moreover, at least two dose constraint points must be applied for bladder and rectum: one close to the midpoint of the total dose and the other close to the total prescription dose²². In 2020, NRG (a non-profit research organization formed by the union of three groups: the National Cancer Trials Network, Radiation Therapy Oncology

Group (RTOG), and Gynaecology Oncology Group) released a consensus contouring guideline that also provides dose constraint recommendations for moderate hypofractionation, which are in keeping with the 2018 joint guideline⁸⁷. These expert-developed resources are invaluable for radiotherapy departments that are beginning to develop their prostate hypofractionation programme and are usually easily accessible even for cancer centres operating within LMICs.

Radiotherapy machines. Either gantry-based LINACs equipped with pre-treatment image guidance capabilities or robotic arm-based devices such as the Cyber-Knife (CK) can be used to deliver moderate hypofractionation or SBRT using megavoltage photons. The CK system offers a greater degree of versatility in beam arrangement as it is not constrained to a single plane of rotation. In addition, CK offers real-time fiducial tracking using kV X-ray fluoroscopy throughout treatment delivery, which can modify the position of the treatment head in accordance with patient motion⁸⁸. Much of the published literature for SBRT stems from experiences using the CK system⁸⁹. A pooled analysis of 1,100 patients from a multi-institutional consortium of prospective phase II trials investigating prostate SBRT reported a 95%, 84% and 81% rate of 5-year BCFS for patients with low-risk, intermediate-risk and high-risk disease, respectively⁹⁰. These oncological outcomes reflect those observed from more protracted treatment courses such as moderate hypofractionation or conventional schedules.

However, CK systems are not as readily available as standard LINAC machines, particularly in LMICs, as their cost can be anywhere within US\$ 3–5 million⁹¹. Furthermore, the treatment times are substantially longer with CK than with standard LINACs (45 versus 15 minutes, on average)⁹². Two studies have compared the treatment plans of patients with low-risk prostate cancer treated with LINAC and CK-based SBRT regimens who were treated with 36.25 Gy in 5 fractions. Investigators found no dosimetric advantage between CK and non-CK techniques and, in fact, reported that LINAC techniques were associated with superior rectum and bladder sparing^{93,94}. Similarly, a systematic review concluded that robotic arm-based and gantry-based SBRT were associated with equivalent biochemical failure and toxicity rates⁹². Importantly, the authors of this study drew attention to the reduced treatment time associated with gantry-based LINACs compared with robotic-arm LINACs, which is a crucial factor to consider in limited-resource settings. Notably, these studies use modern LINACs, in which flattening filter-free technology, which saw widespread adoption by 2010 for stereotactic treatments, enables a reduced treatment time and steeper dose gradient compared with older LINACs. Nevertheless, these data provide strong evidence that SBRT can be safely and effectively performed with the more readily available gantry-based LINAC systems in conjunction with CBCT capacity and that the oncological and toxicity outcomes are not inferior to those observed with CK units.

Finally, evolving evidence suggests that MRI-LINACs can feasibly administer a course of SBRT without

Dose constraint points

Accepted dosimetric values to ensure the safety of normal tissues. Often, these constraints are expressed as a maximal dose limit to a specified volume of a normal tissue.

Megavoltage photons

Megavoltage is the most common energy level used in modern linear accelerators for the treatment of most cancers owing to its deep penetration. Other photon energies, such as kilovoltage or orthovoltage, can be used for superficial cancers such as skin cancers.

fiducial placement^{95–97}. These machines, which have become commercially available since 2018, have adaptive day-to-day online imaging capabilities, enabling treatment adaptation in the event of plan deviations^{98,99}. However, like CK systems, these novel machines are expensive, costing CAD\$ 8.5–10 million¹⁰⁰, and have more limited operational capacity than gantry-based LINACs given their comparatively longer treatment durations (typically ~45 minutes as opposed to typically 20 minutes)¹⁰¹. MR-LINACs are, therefore, not well suited for implementation in the developing world.

Treatment delivery and quality assurance. Intensity modulation has been used in many trials and is becoming more commonly implemented for localized prostate cancer treatment given its superior ability to conform to the target volume and to spare nearby normal tissues (FIGS 1,2). Only one prospective study has been designed to compare IMRT and 3D-conformal radiotherapy (3D-CRT)¹⁰². In this trial, 215 patients treated with 70 Gy in 25 fractions were randomized to receive treatment with either IMRT or 3D-CRT. After 4.6 years' median follow-up duration, IMRT was associated with

lower toxicity rates than 3D-CRT (RTOG grade ≥ 2 late GU toxicity 3.7% and 12.3%, respectively ($p = 0.02$); RTOG grade ≥ 2 late GI toxicity 6.4% and 21.7%, respectively ($p = 0.001$); RTOG grade ≥ 2 early GI toxicity 7% and 24%, respectively ($p = 0.001$); RTOG grade ≥ 2 early GU toxicity 9% and 27%, respectively ($p = 0.001$)). The 5-year rate of BCFS was not different for the IMRT and 3D-CRT groups, at 95.4% and 94.3% ($p = 0.678$), respectively¹⁰². A secondary analysis of the RTOG 0126 trial, which compared IMRT and 3D-CRT in patients with prostate cancer, mirrored these findings, with the IMRT arm experiencing significantly less acute GI and GU toxicity than the 3D-CRT arm (10% and 15%, respectively; $p = 0.042$) as well as grade ≥ 2 late GI toxicity (15% and 22%, respectively; $p = 0.039$). These data suggest that IMRT is superior to 3D-CRT for use in hypofractionated prostate radiotherapy delivery, although 3D-CRT is associated with acceptable toxicity rates and oncological outcomes if IMRT is not available¹⁰³

The management of inter-fraction and intra-fraction variation is one of the main technical challenges in treatment delivery. A robust quality assurance programme combined with a suitable target margin according to the image-guidance approach is critical in ensuring the safe and effective delivery of moderate hypofractionated and SBRT for localized prostate cancer treatment. Target localization can vary and can be dependent on rectal and bladder filling, even while the treatment is being delivered¹⁰⁴. Thus, confirmation of the anatomy is crucial before the delivery of each fraction to avoid a reduction in treatment efficacy and an increase in toxic effects¹⁰⁵. Where IGRT is absent, such as in low-resource settings where LINAC upgrades can be cost prohibitive, a larger margin is required, resulting in much higher doses to nearby structures and organs such as the rectum (FIGS 3,4).

Several options are available to assess prostate displacement during treatment: cine-MRI, electromagnetic transponders such as Calypso system by Varian¹⁰⁶, CBCT, fiducial markers and ultrasonography. Each method has advantages and limitations in terms of cost, precision and treatment time²², but the overall goal with all of these systems is to ascertain the inter-fraction and intra-fraction movement of the prostate to enable the application of smaller PTV margins.

Moderate hypofractionation does not require as stringent image guidance as SBRT given the lower dose per fraction and reduced risk of serious adverse effects if one fraction is sub-optimally targeted. This less-stringent approach is reflected in the PTV margin used (5–10 mm), which is often similar to that of conventionally fractionated plans. As such, alternate image guidance approaches can be considered. The use of CBCT and orthogonal kV–kV with fiducials as image-guidance modalities have been compared in a retrospective study of PTV margin definition. The study showed no difference in the accuracy of target delineation and determined that PTV margins can be kept at 5–8 mm with daily imaging regardless of modality used¹⁰⁷. Furthermore, more than half of patients in the seminal CHHiP trial¹⁶ were not treated with IGRT techniques yet grade 2+ toxicity was only ~12% in the hypofractionated groups despite the

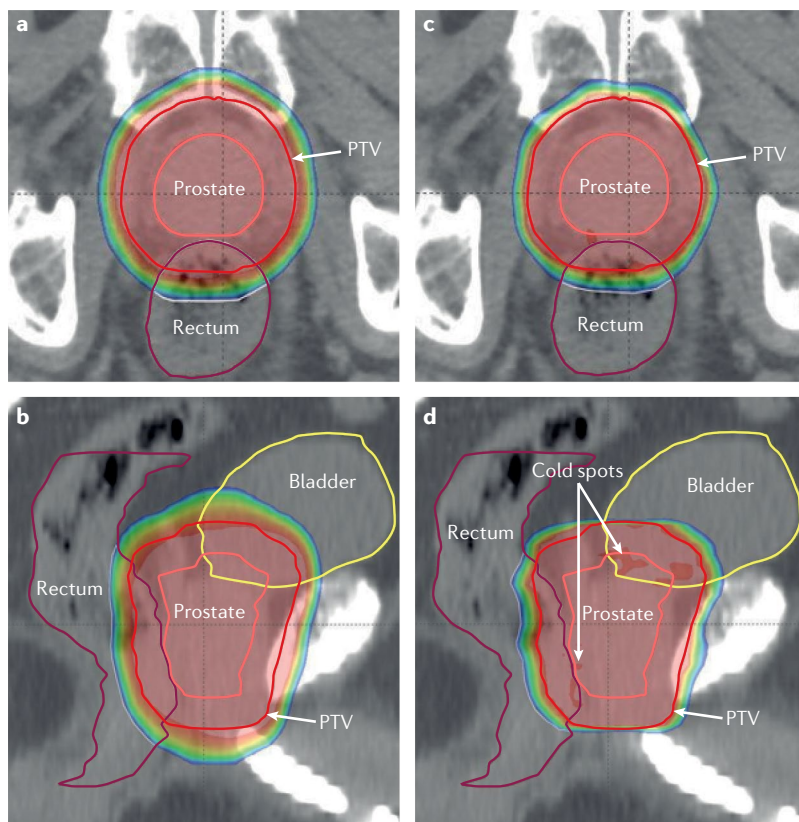


Fig. 1 | Isodose map of moderate hypofractionation plans. A dose colour map of a 3D conformal plan used to treat a prostate target using moderate hypofractionation are depicted in axial (part a) and sagittal planes (part b). For a treatment without the use of margin-reducing techniques like image-guided radiotherapy, a 1 cm planning target volume (PTV) margin is used around the prostate. The use of an intensity-modulated radiotherapy technique, shown in axial (part c) and sagittal (part d) planes, results — for this patient — in a modest reduction on the high-dose region overlapping the bladder and rectum but at the expense of small cold spots within the prostate. For comparative purposes, the white line represents the portion of rectum receiving >85% of the prescribed dose (represented by the dark blue colour on the dose map).

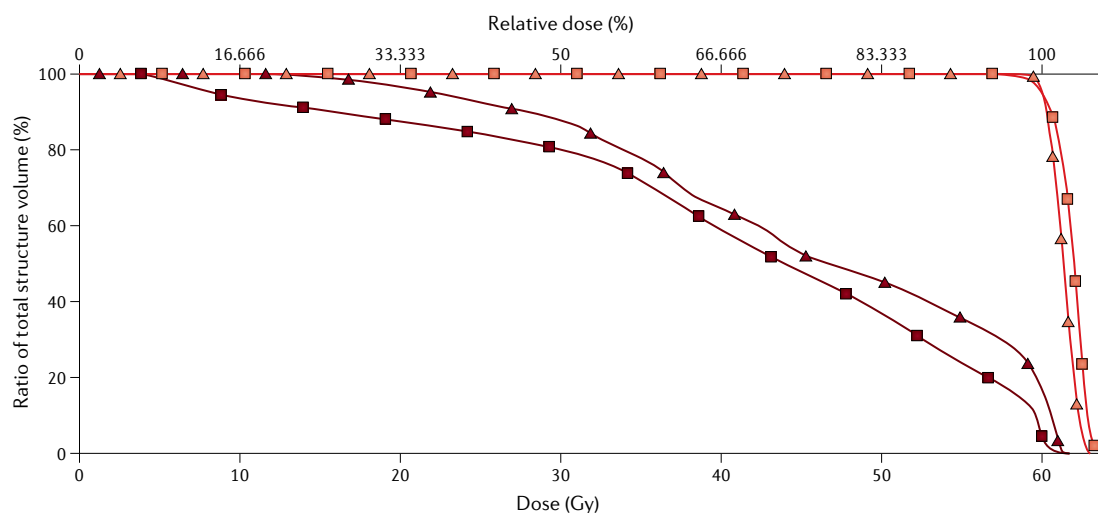


Fig. 2 | Cumulative dose volume histograms (DVH) for moderate hypofractionation. Cumulative DVHs for the planning target volume (red) and rectum (brown) for the 3D treatment plan (triangle) and IMRT (square) plans from FIG. 1 are depicted. The blue circles represent planning criteria for rectal toxicity. In this example, the addition of intensity-modulated radiotherapy (IMRT) was sufficient to meet rectal constraints but with an increase in cold spots inside the target volume.

lack of image guidance. These data suggest that moderate hypofractionation can be safely and effectively delivered without strict IGRT requirements, improving access in centres in LMICs in which the costs of IGRT upgrades can be prohibitive. However, daily IGRT should be encouraged for facilities with this capability, even for moderate hypofractionation.

Techniques to limit inter-fraction variation include controlling bladder and bowel filling with the intake of a defined volume of water¹⁰⁸, the use of laxatives¹⁰⁹, a strict diet throughout the course of treatment¹¹⁰ and immobilization of the prostate using an endorectal balloon¹¹¹. Hydrogel spacers can improve rectal dose and toxicity¹¹². However, despite all these alternatives, the joint AUA/ASCO/ASTRO guideline recommends that, until data from phase III trials are available, each centre should define its IGRT protocol²².

A number of clinical and technical considerations apply to moderate and ultra-hypofractionated treatments (TABLE 2). As per the 2018 joint guidelines, ultra-hypofractionation should be restricted to patients with a prostate volume of <100 cc, International Prostate Symptom Score (IPSS) of <20 and non-high-risk disease as the majority of published prospective evidence supports these specifications²². Trials that are currently in progress, such as the RTOG/NRG GU005 (NCT03367702) trial and the HEAT trial (NCT01794403), further restrict the criterion of prostate volume to be <70 cc and <80 cc, respectively^{113,114}. From a technological perspective, most of the available data for ultra-hypofractionation are derived from patients treated with IMRT. This is due, in part, to the temporal association between the adoption of intensity modulation in localized prostate trials and the novelty of ultra-hypofractionation. IGRT was mandated in both randomized trials of ultra-hypofractionation as were smaller PTV expansions in comparison to moderate hypofractionation studies, which did not have these requirements^{19,20,22}.

For centres in LMICs considering the transition to hypofractionation, several key points must be considered. First, the appropriate treatment machine must be acquired and commissioned. Gantry-based LINAC systems, the most readily available and affordable radiotherapy machines, can be effective for both moderate and ultra-hypofractionated therapies. Newer technologies such as CK or MR-LINACs, although tempting due to their novelty, are not the most economical investment for a department owing to their high initial start-up costs as well as longer treatment duration. Secondly, clear patient preparation and simulation protocols can provide cost-effective methods to improve treatment outcomes. Stringent pre-treatment patient protocols to ensure bladder filling and rectal emptying are inexpensive to establish, easy to implement and can drastically improve target localization, reducing treatment margins and decreasing overall toxicity. Next, the choice of image guidance, if any, must be determined. An option in departments with multiple LINACs is to equip one with onboard CBCT capabilities and subsequently distribute patient load so that interval IGRT can be performed for all patients, for example, on a weekly basis. However, centres interested in ultra-hypofractionation must keep in mind that IGRT is mandatory for each fraction. If initial upgrade costs for IGRT capabilities are prohibitive, moderate hypofractionation can still be performed with reasonable outcomes¹⁶. Finally, treatment planning protocols, including target volume margins and normal tissue tolerances, must be adapted based on IGRT frequency and quality to ensure efficacy and safety.

Cost and cost-effectiveness

Despite the clinical and logistical advantages of hypofractionation, cost and sustainability remain the driving force behind the clinical implementation of new treatment methodologies. Several financial considerations beyond the initial machine purchase cost must

Incremental cost-effectiveness ratio (ICER). A summary measure representing the economic value of an intervention in comparison to an alternative (comparator). The ICER is usually expressed as a monetary amount per quality-adjusted life year.

Quality-adjusted life year (QALY). A measure of disease burden that accounts for the quality and quantity of life lived. QALY scores range from 1 (a year lived in perfect health) to 0 (death). Comorbid conditions will result in a QALY measure that is intermediate to these values.

be examined by a radiotherapy department prior to developing a hypofractionation programme, including machine commissioning, maintenance, power, staffing and training expenses. Economic evaluations are helpful in providing guidance and long-term cost comparisons between different radiotherapy techniques and modalities.

Economic evaluation studies. Developments in radiotherapy, from standard 3D-CRT, IMRT and incorporation of IGRT, have increased the associated costs for each treatment course. These costs are largely associated with the increased labour required to plan, check and administer IMRT treatments and, therefore, the cost is variable amongst health-care systems. In general, the cost of a conventional course of 3D-CRT for localized prostate cancer has been estimated to be approximately CAD\$ 13,500 for each patient, whereas IMRT costs approximately CAD\$ 14,520 for each patient in Canada^{115,116}. In the USA, this cost differential was greater than in Canada, in that 3D-CRT was US\$ 13,013 per course, whereas IMRT cost US\$ 27,084 (REF.¹¹⁷). A British study reported a cost of £ 4,799.31 and £ 5,920.93 for a conventional course of 3D-CRT and IMRT, respectively¹¹⁸. Although IMRT has

a higher nominal cost than 3D-CRT, the incremental cost-effectiveness ratio (ICER) of IMRT was shown to be under the generally accepted range of US\$ 50,000/quality-adjusted life years (QALY) in the USA¹¹⁹ and Canada¹¹⁵ owing to the eventual health economic savings of this modality, which are due, in general, to lower rates of toxicity¹²⁰. Likewise, despite higher initiation costs than conventional radiotherapy and moderate hypofractionation, SBRT shows promise for prostate cancer treatment in terms of both the long-term cost savings associated with this modality and the potential radiobiological benefits for disease control with larger fraction sizes²¹.

A number of economic evaluations have compared conventional, hypofractionated and ultrahypofractionated treatment for localized prostate cancer^{121–126} (TABLE 3). A 2012 study by Hodges et al.¹²⁵ performed a cost–utility comparison between SBRT and conventional IMRT for a model 70-year-old man with localized prostate cancer. In their model, both modalities resulted in a mean QALY of 7.9 years but SBRT was associated with a higher total cost of US\$ 22,152 versus US\$ 35,431 for conventional IMRT. Sensitivity analysis showed that up to a 6% decrease in efficacy and 4% decrease in toxicity outcomes for SBRT was allowed to maintain an ICER of approximately US\$ 50,000 per QALY, which is a commonly accepted willingness-to-pay threshold. Another 2012 US-based study compared the cost utility of conventional IMRT, SBRT and proton therapy. SBRT was found to be the least costly modality with a lifetime cost of US\$ 24,873 versus IMRT (US\$ 33,068) and proton therapy (US\$ 69,412) and resulted in the most QALYs at 8.11 years versus 8.05 and 8.06 years for the same modalities, respectively¹²⁶. In 2014, Sher et al.¹²⁴ compared conventional IMRT versus CK-based SBRT and non-CK-based SBRT using a 65-year-old man with low-risk prostate cancer as a model patient. The authors concluded astounding ICERs of US\$ 285,000 per QALY and US\$ 591,100 per QALY for IMRT over non-CK-based and CK-based SBRT, respectively, suggesting a considerable cost benefit of SBRT over conventional IMRT.

Moderate hypofractionation and SBRT have also been evaluated. A Canadian cost–utility analysis compared conventional, moderate hypofractionated and SBRT treatment schedules in a model 70-year-old man with low-risk prostate cancer. SBRT was ultimately demonstrated to be the most cost-effective option, with a cost of CAD\$ 4,368–6,333 per QALY, compared with CAD\$ 4,956–6,462 and CAD\$ 5,935–7,992 per QALY for moderate hypofractionated and conventional treatment, respectively¹²³. In a secondary analysis of a randomized trial, Voong et al.¹²² reported a difference of US\$ 7,000 at a median of 6 years with conventional (US\$ 30,241) versus hypofractionated IMRT (US\$ 22,957), with no threshold reported within the sensitivity analysis wherein conventional treatment would be less costly. Finally, a Hungarian cost–utility analysis comparing 3D-CRT with conventional and moderately hypofractionated IMRT concluded that, compared with conventional 3D-CRT, conventional IMRT and hypofractionated IMRT resulted in ICERs of €1,624 and €5,600 less per QALY, respectively¹²¹.

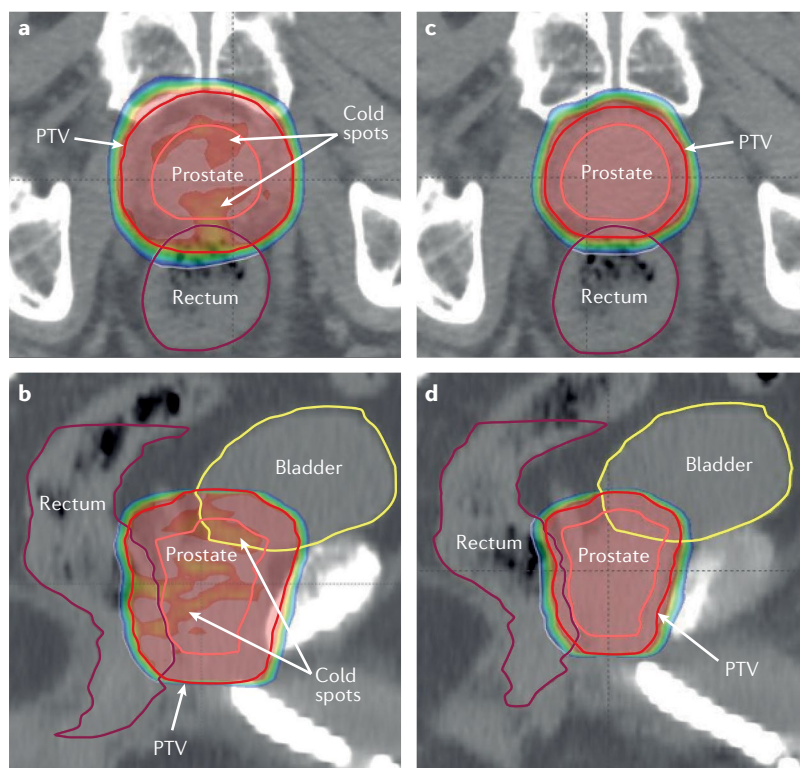


Fig. 3 | Isodose map of ultrahypofractionation plans. A dose colour map for a volumetric modulated arc therapy plan proposed to treat a prostate target using stereotactic body radiotherapy without the use of image-guided radiotherapy (IGRT) (planning target volume (PTV) margin of 1 cm) shown in axial (part a) and sagittal (part b) planes and with the use of IGRT (PTV margin of 0.5 cm) in axial (part c) and sagittal (part d) planes. Despite the use of volumetric modulated arc therapy for delivery, without the use of IGRT, the bladder and rectum doses would be unacceptably high and would result in substantial underdosing of the prostate. For comparative purposes, the white line represents the portion of rectum receiving >85% of the prescribed dose (represented by the dark blue colour on the dose map).

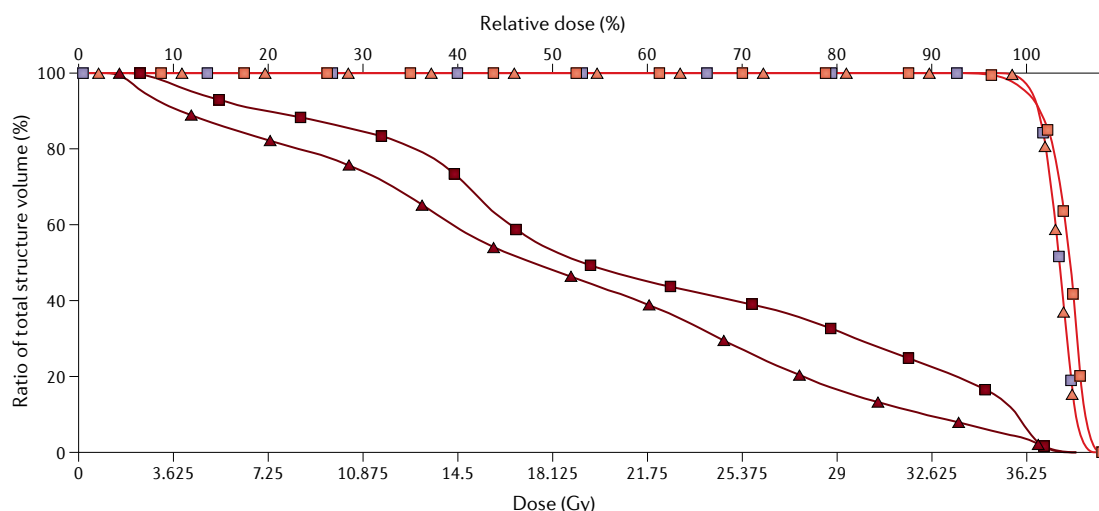


Fig. 4 | **Cumulative dose volume histograms (DVH) for ultrahypofractionation. Cumulative DVHs for the planning target volume (red) and rectum (brown) for the non-image-guided radiotherapy (triangle) and image-guided radiotherapy (square) plans from FIG. 3.** The blue circles represent planning criteria for rectal toxicity. Both plans were produced using volumetric modulated arc therapy. The non-image-guided plan does not meet the rectal criteria despite the use of volumetric modulated arc therapy and results in more substantial underdosing of the target volume.

Furthermore, these observations are supported by real world data. A 2019 Surveillance, Epidemiology, and End Results (SEER) database analysis estimated an annual cost saving of US\$ 160–360 million with the exclusive use of moderate hypofractionation in the USA compared with conventional fractionation¹²⁷. In LMICs, these cost savings could translate to more money being available for equipment acquisition and upgrades, personnel training, and an opportunity to expand the treatment capacity of the centre¹²⁷.

Hardware costs. Image-guidance is necessary to decrease toxicity and improve treatment delivery and, for certain techniques such as SBRT, high-quality image guidance is essential. A 2014 comparison of various image-guided radiotherapy strategies estimated the individual costs of distinct IGRT techniques¹²⁸. In this analysis, the daily costs for cine-MRI, electromagnetic transponders, CBCT, fiducial and ultrasonography were US\$ 3,000–4,000/scan, US\$ 64–141/day, US\$ 143/day, US\$ 87/day and US\$ 67/day, respectively, according to the Medicare fee schedule. The cost of a transponder placement was estimated at US\$ 1,200/patient and fiducial marker placement cost was estimated at US\$ 391/patient.

The additional costs of adjunct technologies for radiotherapy delivery must also be taken into consideration. In 2017, the average price of a LINAC was US\$ 1,976,000 and the inclusion of the equipment required for CBCT cost an additional US\$ 350,000, representing an increase of ~18% in the cost of the machine¹²⁹. As a result, some centres, whether in high-income countries or LMICs, can find the initial cost prohibitive beyond funding of the basic LINAC, restricting the use of hypofractionated strategies such as SBRT, which require additional equipment¹³⁰.

In 2012, in order to address the radiotherapy shortage, the Brazilian government spearheaded a national project to expand LINAC capacity within the country¹³¹.

The initial goal was to expand 32 existing radiotherapy centres and build 48 new centres with a total goal of adding 80 LINACs nationally; however, 8 years after the initiation of the project, only 38 LINACs have been installed and only 29 are operational. Additionally, the goal is now to expand to 100 LINACs total (adding 20 more LINACs to the initial goal of 80) by November 2021, a goal which has been hampered by the COVID-19 pandemic. In Brazil's radiotherapy expansion project, the estimated cost to upgrade a multi-leaf collimator (MLC) from 80 to 120 leaves to enable increased precision in dose shaping and to add IMRT licenses is US\$ 350,000. The upgrade to CBCT capability would add another US\$ 350,000. Acquisition of these upgrades, which are necessary in order to provide SBRT, would result in a total cost that is much higher than a basic LINAC.

Machine upkeep and maintenance costs are additional financial considerations for a radiotherapy programme, which can be particularly burdensome to low-resource centres. A 2021 survey of 28 African countries reported that LINAC downtime in these countries is associated with failures of the vacuum pump, power instability and malfunction of the MLCs¹³². Recurring costs have been estimated to account for a further 5.5–15% of the initial machine investments¹³³. LINAC maintenance and quality assurance (QA) have been estimated to have a median annual cost of US\$ 41,390, with further annual electrical costs of US\$ 2,800 for machine operation. The median cost per fraction of radiotherapy has been calculated as US\$ 11.02 for LINAC machines, which further illustrates the cost benefits of hypofractionation in minimizing these added costs¹³⁴.

Personnel and training costs. Finally, the stringent dosimetric constraints, complex planning requirements and treatment monitoring involved in hypofractionation will require advanced training and departmental protocol development that meets internationally accepted

Table 2 | Clinical and technical requirements of conventional radiotherapy, moderate fractionation and ultra-hypofractionation

Characteristic	Conventional radiotherapy	Moderate hypofractionation	Ultra-hypofractionation
Prostate size	No	No	<100 cc
IPSS cut-off	None	None	<20
Risk stratification	Any risk	Any risk	Low or intermediate risk
Dose per fraction	1.8–2 Gy	<5 Gy	≥5 Gy
IMRT	Encouraged	Recommended	Strongly recommended
IGRT	Recommended	Strongly recommended	Mandatory
PTV expansion	8–10 mm	5–10 mm	3–7 mm

IPSS, International Prostate Symptom Score; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; PTV, planning target volume.

standards set by trial protocols and are in line with the International Commission of Radiation Units and Measures (ICRU)¹³⁵. Radiology departments will be required to fund the additional training required to ensure proper treatment setup and delivery themselves as well as covering the costs of equipment maintenance and QA. Skilled personnel training has been identified as a particular challenge in LMICs, in which human resources are often limited. A 2014 study of radiation therapy infrastructure and human resources in LMICs estimated deficits of 39%, 68% and 67% in radiation oncologists, medical physicists and radiation therapists, respectively; in 2020, they estimated that these same needs would grow to be 103%, 292% and 270%, respectively, of the 2014 capacity²⁹. Often, training must be sought in well-established cancer centres in industrialized countries, which presents further issues. The first of these is the cost of training. The cost of a European-trained team of four radiation oncologists, three medical physicists and seven therapists has been estimated at €1.85–2.516 million, which is prohibitive to most radiation oncology centres in LMICs. Nevertheless, the International Atomic Energy Agency (IAEA) provides grant support for candidates from low-income countries and partial coverage for trainees from middle-income countries to train abroad²⁷. The second issue is of ‘brain drain’, whereby trained professionals opt to emigrate to more industrialized countries after training for better opportunities, resources and QoL. This phenomenon has been identified as a particular issue for medical physicists as they seek support in countries where they are not identified as health professionals, which is commonplace in LMICs¹³⁶. The brain drain phenomenon has been identified as a major concern in the global oncology community and a call to action has been made for developed countries to help LMIC institutions to retain personnel after training by abolishing policies such as merit-based immigration, which involves setting educational and skill requirements for prospective immigrants¹³⁷.

Obstacles and opportunities for LMICs

Despite the advantages of hypofractionation, adoption in LMICs remains low compared with high-income countries¹³⁸. A 2021 international ESTRO survey of

over 2,300 radiation oncologists reported that radiation oncologists from LMICs (OR 0.54; $p < 0.001$) and Asia-Pacific regions (OR 0.47; $p < 0.001$) were significantly less likely to use hypofractionation on multi-variable analysis than Europeans. In prostate cancer treatment specifically, respondents practicing in the Middle East and Africa reported the lowest rates of hypofractionation utilization (18–30%) despite also being nations in which resource limitations are high. The authors of the study raise concerns that a knowledge gap existed, particularly in Africa, where respondents had the lowest acceptance of hypofractionation but, conversely, the highest support for controversial indications such as elective pelvic irradiation¹³⁸. Provider education is an important consideration in the implementation and acceptance of a hypofractionation programme and, as such, just as critical to the development of a hypofractionation programme as the technical infrastructure.

Opportunities for improvement. As global access to the internet expands, e-learning approaches provide a promising and robust platform for educational opportunities between developed and developing countries. For example, the Africa Radiation Oncology Network (AFRONET) coordinated by the IAEA, enables radiation oncology trainees from Anglophone African countries to learn from international experts in the field¹³⁹. Several other professional organizations, including ASTRO and the American Association of Physicists in Medicine (AAPM), have developed online training modules specifically geared towards LMICs in order to extend opportunities for education, cancer care, research and outreach to developing nations¹⁴⁰. The radiation oncology community is encouraged to take advantage of information and communication technologies (ICTs) in order to extend opportunities for education, cancer care, research and outreach to developing nations¹⁴¹. In particular, ICT platforms can enable educational sessions and resources to be shared from established oncology centres in developed countries with developing centres in LMICs. In 2019, experts from the UK and Canada, in consultation with the IAEA, led a 4.5-day web-based programme on the target volume delineation in the treatment of prostate cancer. It was attended by 22 participants from 11 African LMICs. Participants were able to participate in 1:1 tutorials to consolidate their learning and, in some cases, produce acceptable target volume and normal tissue contours, with only minor revision required¹⁴². Furthermore, in day-to-day operations, cloud-based technology could be used for plan review, whereby experts from established centres can offer aid and opinions on more complex plans remotely^{141,143}.

Several other ICT-powered programmes are currently in existence¹⁴⁴. **BOTSOGO** is a collaborative effort between Harvard Medical School and the oncology community of Botswana, which includes monthly tumour boards as well as guidance on developing a local research infrastructure¹⁴⁵. **Radiating Hope**, a non-profit organization dedicated to updating and providing radiotherapy equipment to developing countries, has developed a

remote platform to enable treatment planning QA and technical support^{144,146}. The Quality Assurance Review Centre (QARC) is a US-based programme from the University of Massachusetts Medical School that provides remote radiotherapy plan QA as well as clinical trial support for developing countries¹⁴⁴. *Global RT* is an online forum for the education and discussion of the essential nature of radiotherapy for the global community, which also lists global oncology opportunities for interested volunteers¹⁴⁷.

As machine learning (ML) and artificial intelligence technologies evolve, the development of machine-assisted planning also offers an opportunity for LMICs. In 2019, the first patient with localized prostate cancer was treated with IMRT via a machine-generated plan as part of a clinical trial in Canada¹⁴⁸. Since then, substantial focus has been directed towards advancing these technologies in the field of radiation oncology. Not only does the use of ML-based planning algorithms expand the capacity for patient treatment but it might also support the training of inexperienced personnel and guide them through the planning process without the need for direct supervision. Furthermore, ML can facilitate plan QA, a process in most centres in which new radiotherapy plans are reviewed by the departmental group for safety and quality. In this way, centres with limited personnel can focus their human resources on reviewing only on the cases with the most complex concerns necessitating group discussion¹⁴⁹. A 2020 perspective piece by Australian radiation therapists urged

that ML education be incorporated in radiation therapy training programmes as its role in patient care expands and is substantiated¹⁵⁰; however, at the time of writing, the field of ML and its application to radiotherapy is still in its infancy. Further refinement of these technologies is required before regular practice implementation can occur in developed countries with sufficient personnel oversight and, subsequently, in LMICs.

Modelling the impact of prostate hypofractionation

The potential for increasing access to radiotherapy by using moderate hypofractionation and/or SBRT in the treatment of localized prostate cancer can be illustrated with a real-life working example. A 2013 analysis of African radiotherapy resources by the IAEA identified Nigeria as needing the most additional machines (138 machines) to adequately service their population²⁸. Thus, the potential benefits of hypofractionation in Nigeria can be used to model the effects of hypofractionation rollout in other LMICs.

Capacity. This model begins with a number of assumptions. According to the IAEA directory of radiotherapy centres, as of 2020, Nigeria has seven linear accelerators to service the entire country¹⁵¹. Each radiotherapy unit is estimated to treat 400–600 patients a year for all indications^{37,152}. Given that a course of conventional radiotherapy for prostate cancer tends to be longer than most other radiotherapy treatments¹⁵³, usually requiring 38–39 daily fractions, the lower end of 400 patients is a reasonable capacity estimate per radiotherapy machine per year. By contrast, moderate hypofractionation will be assumed to be 20 daily fractions and SBRT to be 5 daily fractions as per CHHiP/PROFIT and PACE-B schedules. According to the GLOBOCAN database, a total of 15,306 cases of prostate cancer were reported in Nigeria in 2020 (REF.²), which, when considering previous series reporting that nearly 60% of patients presenting for care in southwestern Nigeria had metastatic stage at presentation^{154,155}, means that 6,122 (40%) patients annually would require radical treatment for localized prostate cancer. For the purposes of this example, we assume that all patients will be eligible for radical radiotherapy and that prostatectomy will not be considered as a competing treatment modality.

Considering all assumptions, a total of 2,800 prostate cancer patients (46% of all incident prostate cancers per year) can be treated annually with conventional treatment using Nigeria’s current machine capacity, before even considering the use of the machine to treat other malignancies that ‘compete’ for radiotherapy resources. The implementation of hypofractionation would translate into a twofold increase in capacity, without any additional investment. SBRT has the most drastic effect, with a treatment course that requires only one-eighth of the fractions needed for a conventional course. The implementation of SBRT would, therefore, mean that nearly all patients would be able to access curative therapy. Thus, the benefit of using hypofractionation to increase the proportion of patients who will be able to receive curative intent radiotherapy is clear.

Table 3 | Cost effectiveness of hypofractionation and SBRT versus conventional radiotherapy

Study	Country	Study details	Economic evaluation
Hodges et al. ¹²⁵ (2012)	USA	Cost–utility; 10-year time horizon; IMRT vs SBRT	Cost per treatment: SBRT US\$ 22,152, IMRT US\$ 35,431; mean QALY of 7.9 for both modalities
Parthan et al. ¹²⁶ (2012)	USA	Cost–utility; lifetime time horizon; IMRT vs protons vs SBRT	Lifetime cost: SBRT US\$ 25,097, IMRT US\$ 35,088, proton therapy US\$ 71,657; SBRT strongly dominates IMRT and protons
Sher et al. ¹²⁴ (2014)	USA	Cost–utility; lifetime time horizon; IMRT vs SBRT	ICER (per QALY): robotic SBRT vs IMRT US\$–285,000, non-robotic SBRT vs IMRT US\$–591,100
Sharieff et al. ¹²³ (2016)	Canada	Cost–utility; lifetime time horizon (20 years); IMRT vs HF-IMRT vs SBRT (Robotic vs LINAC vs arc-based)	Cost per QALY (fixed arc-LINAC based): conventional CAD\$ 5,935–7,992, HF-IMRT CAD\$ 4,956–6,462, SBRT CAD\$ 4,368–6,333
Voong et al. ¹²² (2017)	USA	Cost-minimization; lifetime time horizon; IMRT vs HF-IMRT	Cost per treatment: IMRT US\$ 30,241, HF-IMRT US\$ 22,957
Zemplenyi et al. ¹²¹ (2018)	Hungary	Cost–utility; 10-year time horizon; 3D-CRT vs IMRT vs HF-IMRT	ICER (per QALY): IMRT vs 3D-CRT €–1,624, HF-IMRT vs 3DCRT €–5,600; both strongly dominating

3D-CRT, three-dimensional conformal radiotherapy; HF-IMRT, hypofractionated intensity-modulated radiotherapy; ICER, incremental cost effectiveness ratio; IMRT, intensity-modulated radiotherapy; LINAC, linear accelerator; QALY, quality-adjusted life year; SBRT, stereotactic body radiotherapy.

Cost. According to a 2016 economic analysis that directly compared the costs of a conventional, hypofractionation and ultra-hypofractionated schedule, the total cost of treating all 2,800 patients with arc-based conventional fractionation would be CAD\$ 16,618,000 (US\$ 12.6 million)¹²³. By contrast, hypofractionation and SBRT with the same arc-based system would cost CAD\$ 13,876,800 and CAD\$ 12,230,400, respectively, for these same 2,800 patients. This difference amounts to a total cost-saving of almost CAD\$ 3 million and CAD\$ 4.5 million with hypofractionation and ultra-hypofractionation, respectively, compared with a conventional fractionation schedule. However, the start-up costs associated with machine upgrade and personnel training must also be considered, although personnel training can be covered by the IAEA programme for trainees from LMICs. Assuming that each LINAC requires MLC and CBCT upgrades (which are estimated to cost US\$ 700,000 as per the Brazilian report¹³¹) to provide optimal hypofractionation treatment, the cost would total US\$ 4.9 million (CAD\$ 6.25 million). Thus, using moderate hypofractionation the initial capital invested in upgrading these LINACs would break even in a little over 2 years and the costs would be recouped in less than 2 years for SBRT. Notably, although IMRT and CBCT capabilities are ideal for moderate hypofractionation, they are not mandatory and, therefore, represent an area of initial cost-savings that could lead to faster recoupment of overall costs. Thus, by lobbying government agencies for increased funding and device manufacturers to lower acquisition costs for LINACs, the necessary infrastructure can be established in LMICs such as Nigeria, and these countries could expect to offer curative treatment options to more patients with localized prostate cancer in a sustainable manner.

These data are in line with a modelling analysis on the cost savings of switching from conventional to moderate hypofractionation in African countries, which predicted an even greater financial benefit of hypofractionation. This study used an activity-based costing model, which comprehensively accounted for

optimal allocation algorithms to treatment machines as well as personnel salaries, consumable resources, and costs of construction and maintenance. Over a span of 5 years (2019–2025), Nigeria would be expected to save US\$ 91.2 million in total (about US\$ 13 million a year) if considering factors beyond machine and treatment costs such as maintenance and education¹⁵⁶.

The population level benefits of hypofractionation can also extend to upper-middle income countries. In 2016, in the Brazilian public health system, 27,757 patients with intermediate-risk and high-risk prostate cancer were in need of definitive treatment with radiotherapy. Nevertheless, only 53.4% of this population are estimated to have received radiotherapy in this system, resulting in a projected death of 562 patients with intermediate-risk prostate cancer and of 298 with high-risk disease in the 10–13 years from diagnosis³¹. Considering that, in 2016, all patients in the Brazilian public health system were treated using a conventionally fractionated radiotherapy regimen (74 Gy in 37 fractions), almost the entire prostate cancer population (98.8%) requiring radiotherapy in that year could have been treated by the adoption of moderate hypofractionation radiotherapy (60 Gy in 20 fractions).

Conclusions

Evolving evidence supports the efficacy and safety of moderate hypofractionation and ultra-hypofractionation in the management of localized prostate cancer. With resource allocation being a key consideration in LMICs, abbreviating treatment times can alleviate health-care burden and costs to both providers and patients. Hypofractionated regimens can be delivered without substantial added costs to current radiotherapy programmes and, in the long term, have proven more cost-effective. As the world population ages and prostate cancer becomes more prevalent, radiotherapy providers should be encouraged to consider the timely adoption of these treatment schedules.

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M.Y., A.G.G., N.M., V.F.B., L.C.M. and F.Y.M. researched data for the article. A.G.G., F.L.C., L.C.M. and F.Y.M. made substantial contributions to discussions of content. M.Y., A.G.G., F.L.C., N.M., V.F.B., H.P., A.B. and F.Y.M. wrote the article. All authors reviewed and/or edited the manuscript before submission.

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