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Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline

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ASSOCIATED CONTENT

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INTRODUCTION

Background

External beam radiation therapy (EBRT) is a standard definitive treatment option for men with localized prostate cancer and confers long-term prostate cancer control outcomes equivalent to radical prostatectomy.[1] Improvements in imaging and computing over the past two decades have led to a number of technical advances in planning and delivery of prostate EBRT. Notably, these include the use of cross-sectional imaging for treatment planning[2] and innovations in treatment delivery, including intensity modulation[3] and daily image guidance.[4] These technical advances have permitted more precise and conformal delivery of escalated doses of radiation to the prostate, thereby improving the therapeutic ratio.

Classically, the probability of cell survival following a dose of ionizing radiation is governed by the linear-quadratic model. In this model, curves of cell survival as a function of dose have an initial linear component followed by a steeper quadratic component. The relative weighting of each component, and thus the sensitivity to fractionation of the irradiated tissue, is characterized by a parameter called the alpha-beta ratio. The alpha-beta ratio of adenocarcinoma of the prostate is considered low compared to most other neoplasms, with several estimates derived from large populations in the range of 100 to 200 cGy.[5-7] Unlike other solid tumors with higher alpha-beta ratios, the alpha-beta ratio of the adjacent dose-limiting normal structure, namely the rectum, has been estimated to be *greater* than that of prostate cancer itself.[8,9] An implication of this relationship is that hypofractionation—daily delivery of EBRT with fraction sizes > 200 cGy—may further improve the therapeutic ratio of EBRT in localized prostate cancer. Specifically, according to the model, for courses of conventionally fractionated and hypofractionated EBRT that are isoeffective, the hypofractionated regimen would be expected to produce somewhat less toxicity. For courses of conventionally fractionated and hypofractionated EBRT that are isotoxic, the hypofractionated regimen would be expected to be somewhat more effective.

Definitions

Conventional fractionation is defined as EBRT with a fraction size of 180 to 200 cGy. In this guideline, hypofractionation is subdivided into "moderate hypofractionation" and "ultrahypofractionation." As fraction size is a continuous variable, it is acknowledged that hypofractionation represents a spectrum and that any subdivision is necessarily arbitrary, with no universally accepted definitions. The subdivision chosen by the task force reflects the reality that two distinct approaches to hypofractionation have arisen in clinical practice. Moderate hypofractionation is defined in this guideline as EBRT with a fraction size between 240 cGy and 340 cGy. This is a pragmatic definition, and the dose range chosen has been influenced by the approaches used in a number of recently completed large trials that are discussed in detail later.

Ultrahypofractionation is defined in this guideline as EBRT with a fraction size ≥ 500 cGy. The choice of 500 cGy as the cutpoint reflects a body of literature suggesting this is a threshold beyond which the linear-quadratic model ceases to be valid.[10] Ultrahypofractionation has been referred to in the literature alternately as "extreme hypofractionation," "stereotactic body radiation therapy" (SBRT), and "stereotactic ablative body radiation therapy" (SABR), with the latter terms implying particular radiation techniques. Ultrahypofractionation was chosen as a neutral term that stipulates a fraction size but is independent of considerations of technique. The fraction size "gap" created by our definitions (i.e., > 340 cGy

but < 500 cGy) represents a relatively little studied and little used intermediate range that is outside of the scope of the current document. Abbreviations used in the guideline are defined in the Appendices (online only).

Motivation and Scope for Guideline

Given the radiobiological considerations noted above, hypofractionated EBRT has been intensively studied by numerous institutions and cooperative groups in prospective clinical trials in localized prostate cancer. Several large randomized controlled trials (RCTs) comparing conventional fractionation with moderate hypofractionation have been published. At the same time, population-based studies have observed an increasing use in routine practice of ultrahypofractionated EBRT.[11] In this context, the American Society for Radiation Oncology (ASTRO), in collaboration with the American Society of Clinical Oncology (ASCO) and the American Urological Association (AUA), initiated development of an evidence-based clinical practice guideline on hypofractionated EBRT in localized prostate cancer.

The aim of the guideline is to provide recommendations on the use of moderate hypofractionation and ultrahypofractionation with particular reference to oncologic outcomes, toxicity, and quality of life. Hypofractionated radiation has the advantage of shortening treatment duration, is respectful of resource utilization, and appears cost-effective. While health economic endpoints were not directly considered, it is recognized that the very nature of hypofractionation is such that there are potential advantages in terms of cost and convenience for patients.[12,13]

Optimal management of localized prostate cancer is complex and controversial and depends upon life expectancy, risk of progression, and patient preferences. Most practitioners agree that active surveillance is the preferred management strategy for patients with low-risk disease and agree that there is clinical equipoise between radiation and radical prostatectomy with respect to oncologic outcomes among men who require treatment for higher risk cancers or prefer treatment in the setting of low-risk disease.[14] Therefore, the recommendations herein apply to men who require or prefer treatment instead of surveillance and who have opted for EBRT instead of radical prostatectomy, brachytherapy, or other treatment options.

Lastly, for the purposes of this guideline, modulated EBRT techniques are considered broadly to include treatment delivery technologies such as geometrically optimized modulation using robotic linacs with small "beamlet" apertures and other conventionally intensity modulated treatment methods described in the relevant American Medical Association Current Procedural Terminology descriptors.

This guideline is endorsed by the Society of Urologic Oncology, European Society for Radiotherapy & Oncology (ESTRO), and Royal Australian and New Zealand College of Radiologists.

METHODS AND MATERIALS

Process

The ASTRO Board of Directors approved creation of an evidence-based guideline on moderately and ultrahypofractionated EBRT for localized prostate cancer in October 2016. A task force of radiation oncologists, medical physicists, and urologic surgeons/oncologists was recruited. Members were drawn from academic settings, community practice, and the Veterans Affairs system. A radiation oncology resident and a patient representative were also included (see Appendix 1 for thoughts from the patient representative).

Through a series of conference calls and emails, the task force and ASTRO staff refined the key questions (KQs), completed the systematic review, created evidence tables, and formulated the recommendation statements and narratives for the guideline. The task force members were divided into writing groups by KQ according to their areas of interest and expertise. The initial draft was reviewed by six expert reviewers (see Acknowledgements) and ASTRO legal counsel. A revised draft was placed on the ASTRO website for public comment in October and November 2017. Following integration of the feedback, the final guideline was approved by the three societies. The ASTRO Guidelines Subcommittee will monitor this guideline for updating as additional data have been published and presented since the end of the literature review for this project and an update in the near term is anticipated.

Literature Review

A systematic literature review formed the basis of the guideline. An analytic framework incorporating the population, intervention(s), comparator(s), and outcome(s) (PICO) was used to develop search strategies in

Table 1. KQs in PICO Format

Population	*Intervention*	*Comparator*	*Outcomes*
Men with localized prostate cancer who: • Require or prefer treatment instead of active surveillance • Have opted for EBRT instead of prostatectomy, brachytherapy, or other treatment options	KQ1: Moderate hypofractionation	Conventional fractionation	• Prostate cancer control • Toxicity • Quality of life
	KQ2: Different moderate hypofractionation regimens compared with one another		
	KQ3: Ultrahypofractionation	Conventional fractionation	
	KQ4: Different ultrahypofractionation regimens compared with one another		
	KQ5: Different normal tissue constraints used in clinical trials		
	KQ6: Different treatment volumes used in clinical trials		
	KQ7: Moderate or ultrahypofractionation using image guided radiation therapy (IGRT)	Moderate or ultrahypofractionation without IGRT	
	KQ8: Moderate or ultrahypofractionation using intensity modulated radiation therapy (IMRT)	Moderate or ultrahypofractionation using 3-dimensional conformal radiation therapy (3-D CRT)	

MEDLINE PubMed for the KQs. Table 1 lists the KQs in PICO format. The searches identified English-language studies between December 1, 2001 and March 31, 2017 that evaluated men with localized prostate cancer receiving hypofractionated EBRT. Both Medical Subject Headings (MeSH) terms and text words were utilized and terms common to all searches included: *prostate cancer*; *prostate carcinoma*; *prostatic neoplasms[MeSH]*; *localized*; *localised*; *organ-confined*; *early*; *low risk*; *intermediate risk*; *high risk*; *radiation;* and *radiotherapy*. Additional terms specific to the KQs were also incorporated. The three-group risk stratification system as originally proposed by D'Amico, which remains widely used in clinical practice, was adopted.[15] The outcomes of interest were prostate cancer control (including biochemical and clinical recurrence-free survival, disease-specific survival, and overall survival), acute and late toxicity, and quality of life. Hand searches supplemented the electronic searches.

A total of 480 abstracts were retrieved and screened by ASTRO staff and the task force. Subsequently, 419 articles were eliminated based on the exclusion criteria and the restrictions on study design and size. The exclusion criteria included post-operative radiation; high-dose-rate brachytherapy; locally advanced or metastatic disease; salvage therapy or re-irradiation; pre-clinical or non-human studies; dosimetric studies without clinical outcomes; and otherwise not relevant to the KQs. Only studies where hypofractionated EBRT was delivered to the prostate with or without inclusion of the seminal vesicles were included; studies concerning hypofractionated delivery of EBRT to the pelvic lymph nodes were ineligible. Considerations on the use of elective pelvic nodal EBRT in localized prostate cancer are outside the scope of this guideline. Similarly, considerations on the use of androgen deprivation therapy (ADT) in conjunction with hypofractionated EBRT are outside of the scope of this guideline; clinicians are referred to other evidence-based clinical practice guidelines that have issued recommendations on the use of neoadjuvant or adjuvant ADT with conventionally fractionated EBRT.[16-18]

For studies addressing moderately hypofractionated EBRT, only RCTs or meta-analyses of RCTs were included. For those looking at ultra-hypofractionated regimens, RCTs, meta-analyses, and prospective observational studies with at least 50 patients were accepted. Ultimately, 61 articles were included and abstracted into detailed tables to provide supporting evidence for the guideline recommendations.

Relevant abstracts from ASTRO, ASCO, ESTRO, and European Cancer Organisation (ECCO) meetings between January 2014 and January 2017 that fit the inclusion and exclusion criteria and study restrictions were also identified. In some cases, these abstracts are discussed in the narrative, but they were not used to support the recommendations.

PICO

Table 1.

Grading of Evidence and Recommendations and Consensus Methodology

Guideline recommendation statements were developed based on the literature using a modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, which is an explicit, systematic approach to defining the recommendation strength and quality of evidence.[19,20] When available, high-quality data formed the basis of the statements in accordance with the National Academy of Medicine (formerly Institute of Medicine) standards.[21] When necessary, expert opinion supplemented the evidence.

Recommendations were classified as "strong" or "conditional." A strong recommendation indicates the task force was confident the benefits of the intervention clearly outweighed the harms, or vice-versa, and "all or almost all informed people would make the recommended choice for or against an intervention." Conditional recommendations were made when the balance between risks and benefits was more even or was uncertain. In these cases, the task force believed "most informed people would choose the recommended course of action, but a substantial number would not" and, therefore, "clinicians and other health care providers need to devote more time to the process of shared decision making by which they ensure that the informed choice reflects individual values and preferences."[19]

The quality of evidence underlying each recommendation statement was categorized as high, moderate, low, or very low. These quality levels indicated:

- "High: We are very confident that the true effect lies close to that of the estimate of the effect,
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different,
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect,
- Very Low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate."[20]

Consensus was evaluated through a modified Delphi approach based on the ASCO process.[22] In an online survey, task force members rated their agreement with each recommendation on a five-point Likert scale, from strongly disagree to strongly agree. A pre-specified threshold of $\geq$ 75% of raters selecting "agree" or "strongly agree" indicated consensus was achieved. If a recommendation statement did not meet this threshold, it was edited and resurveyed. Recommendation statements that achieved consensus that were modified after the first round were also resurveyed.

KEY QUESTIONS AND RECOMMENDATIONS

Key Question 1

In patients with localized prostate cancer who are candidates for EBRT, how does moderately hypofractionated EBRT (240-340 cGy per fraction) compare to conventionally fractionated EBRT (180-200 cGy per fraction) in terms of prostate cancer control, toxicity, and quality of life based on:

- Prostate cancer risk stratification group?
- Patient age, comorbidity, anatomy (e.g., prostate gland volume), and baseline urinary function?

Prostate cancer control outcomes: Impact of risk stratification group.

Statement KQ1A: In men with low-risk prostate cancer who decline active surveillance and receive EBRT to the prostate with or without radiation to the seminal vesicles, moderate hypofractionation should be offered.

- **Recommendation strength**: Strong
- **Quality of evidence**: High
- **Consensus**: 100%

Statement KQ1B: In men with intermediate-risk prostate cancer receiving EBRT to the prostate with or without radiation to the seminal vesicles, moderate hypofractionation should be offered.

- **Recommendation strength**: Strong
- **Quality of evidence**: High
- **Consensus**: 100%

Statement KQ1C: In men with high-risk prostate cancer receiving EBRT to the prostate, but not including pelvic lymph nodes, moderate hypofractionation should be offered.

- **Recommendation strength**: Strong
- **Quality of evidence**: High
- **Consensus**: 94%

Table 2. Select Randomized Trials Comparing Moderate Hypofractionation to Conventionally Fractionated Radiation (KQ1 and 2)

Trial	N	Median Follow-Up	Design	Study Arms/ EQD2*	Technique	Cancer Risk Groups	Treatment Target	ADT Use and Duration (median)	Age (median)	Comorbidity	Cancer control (Hazard ratio – 1°endpoint)	Acute G2+ GI Toxicity	Acute G2+ GU Toxicity	Late G2+ GI Toxicity	Late G2+ GU Toxicity	Patient-reported outcomes
CHHiP[23]	3,216	5.2 years	Multicenter non-inferiority trial 1°endpoint: biochemical or clinical failure-free rate Non-inferiority margin: hazard ratio 1.208	7,400 in 200 cGy/ 7,400 cGy 6,000 in 300 cGy/ 7,700 cGy 5,700 in 300 cGy/ 7,300 cGy	IMRT IGRT optional (53% use)	15% LR 73% IR 12% HR	Prostate + proximal SV	97% 3-6 mo. (median 5.5 mo.)	68 years	Diabetes: 11% Hypertension: 40% Inflammatory bowel disease: 4% Previous pelvic surgery: 8% Symptomatic hemorrhoids in past 12 months: 7% Previous TURP: 8%	6,000 vs. 7,400 cGy: 0.83 (90% CI: 0.64-1.14) 5,700 vs. 7,400 cGy: 1.20 (90% CI: 0.99-1.46)	25% 38% 38% p<0.0001)	46% 49% 46% (P = 0.90)	14% 12% 11% (5-year)	9% 12% 7% (5-year; 7,400 vs. 6,000 cGy: P = 0.07)	Bowel bother: 14%, 15%, 15% Bladder bother: 17%, 17%, 16% Sexual bother: 52%, 52%, 53% (5-year)
HYPRO[24-26]	820	5 years	Multicenter superiority 1°endpoint: relapse free survival	7,800 in 200 cGy/ 7,800 cGy 6,460 in 340 cGy (3/week)/ 8,700 cGy	IMRT IGRT	26% IR 74% HR	Prostate +/- SV	67% Variable duration (median 32.4 mo.)	71 years 70 years	TURP: 11% (conv), 9% (hypofx) Abdominal surgery: 27%, 23% GI comorbidity: 10%, 9%	0.86 (95% CI: 0.63-1.16)	31% 42% (OR 1.6, 95% CI: 1.19-2.14)	58% 61% (OR 1.12, 95% CI: 0.84-1.49)	18% 22% (3-year; OR 1.19, 95% CI: 0.88-1.59)	39% 41% (3-year OR 1.16, 95% CI: 0.98-1.38)	Not reported
PROFIT[27]	608	6 years	Multicenter non-inferiority trial 1°endpoint: biochemical-clinical failure Non-inferiority margin: hazard ratio 1.32	7,800 in 200 cGy/ 7,800 cGy 6,000 in 300 cGy/7,700 cGy	IMRT or 3-D CRT IGRT required	All IR	Prostate +/- proximal SV	None	71 years 72 years	History of MI: 12% (conv), 9% (hypofx) Diabetes:18%, 16%	0.99 (90% CI: 0.83-1.19)	10% 16% (P = 0.003)	27% 27%	11% 7% (P = 0.006)	19% 20%	Not reported
RTOG 0415[28]	1,115	5.8 years	Multicenter non-inferiority trial 1°endpoint: disease-free survival Non-inferiority margin: hazard ratio 1.52	7,380 in 180 cGy/ 70 7,000 in 250 cGy/8,000 cGy	IMRT or 3-D CRT IGRT required	All LR	Prostate	None	67 years	Not reported	0.85 (95% CI: 0.64-1.14)	10% 11%	27% 27%	14% 22% (P = 0.002)	23% 30% (P = 0.06)	Not reported
Fox Chase[29,30]	303	5.7 years	Single institution superiority trial 1°endpoint: biochemical disease-free survival	7,600in 200 cGy/ 7,600 cGy 7,020 in 270 cGy/8,400 cGy	IMRT u/s IGRT	66% IR 33% HR	IR: Prostate + proximal SV HR: Prostate + SV + LN	46% (median not reported)	Not reported	Not reported	1.38 (95% CI: 0.79-2.40)	Not reported	Not reported	16% 11% (8-year; P = 0.96)	25% 40% (8-year; P = 0.24)	IPSS similar early after EBRT
MD Anderson[31,32]	206	5 years 8.4 years^	Single institution superiority trial 1°endpoint: failure-free survival	7,560 in 180 cGy/ 7,100 cGy 7,200 in 240 cGy/8,000 cGy	IMRT u/s or kV IGRT	28% LR 71% IR 1% HR	Prostate + proximal SV	24% ≤4 mo. (median not reported)	67 years	Not reported	Not reported	Not reported	Not reported	5% 10% (5-year; P = 0.10)	16% 16% (5-year: P = 0.98)	Bowel, urinary, and sexual function similar btw arms (p>0.01)
Italian[33]	168	9 years	Single institution superiority trial 1°endpoint: late toxicity	8000 in 200 cGy/ 8,000 cGy 6,200 in 310 cGy/8,100 cGy	3-D CRT	All HR	Prostate + SV	All 9 mo. (median not reported)	75 years	Not reported	0.62 (95% CI: 0.34-1.14)	21% 35% (P = 0.07)	40% 45% (P = 0.45)	15% 13% (P = 0.57)	21% 14% (P = 0.68)	Not reported

1° = primary; ADT = androgen deprivation therapy; btw = between; CI = confidence interval; conv = conventional fractionation; EQD2 = equivalent dose at 200 cGy; EBRT = external beam radiation therapy; G2+ = grade 2 or higher; cGy = centrigray; HR = high-risk; hypofx = hypofractionated; IPSS = International Prostate Symptom Score; IR = intermediate-risk; LN = lymph nodes; LR = low-risk; MI = myocardial infarction; mo. = months; OR = odds ratio; SV = seminal vesicles

*a/b=1.5

^abstract only

Four large prospective RCTs that enrolled over 6,000 patients, as well as additional single institution RCTs, demonstrate that EBRT delivered to the prostate using moderate hypofractionation (240 to 340 cGy fractions) provides early prostate cancer control that is similar to EBRT delivered using conventional fractionation (180 to 200 cGy per day) (Table 2).[23-33]

The largest multicenter trials are the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) trial, Prostate Fractionated Irradiation Trial (PROFIT), Radiation Therapy Oncology Group (RTOG) 0415 trial, and the Dutch Hypofractionated versus Conventionally Fractionated Radiotherapy for Patients with Prostate Cancer (HYPRO) trial.[23,26-28] The CHHiP trial randomized 3216 men with predominantly intermediate-risk disease to one of three arms: 7,400 cGy in 37 fractions of 200 cGy over 7.4 weeks, 6,000 cGy in 20 fractions of 300 cGy over 4 weeks, or 5,700 cGy in 19 fractions of 300 cGy over 3.8 weeks. At a median follow-up of 5.2 years, the 6,000 cGy hypofractionated regimen had non-inferior biochemical and clinical failure compared to the 7,400 cGy conventionally fractionated regimen. The 5,700 cGy hypofractionated regimen, however, was not non-inferior to the 7,400 cGy regimen with respect to this endpoint.[23]

The PROFIT trial randomized 1206 men with intermediate-risk prostate cancer to either 7,800 cGy in 39 fractions of 200 cGy over 7.8 weeks or 6,000 cGy in 20 fractions of 300 cGy over 4 weeks. At a median follow-up of six years, the hypofractionated regimen had non-inferior biochemical-clinical failure.[27]

RTOG 0415 randomized 1,115 men with low-risk prostate cancer to 7,380 cGy in 41 fractions of 180 cGy over 8.2 weeks or 7,000 cGy in 28 fractions of 250 cGy over 5.6 weeks. At a median follow-up of 5.8 years, the hypofractionated regimen had non-inferior disease-free survival.[28]

Finally, the Dutch HYPRO trial randomized 820 men with predominately high-risk prostate cancer to either 7,800 cGy in 39 fractions of 200 cGy delivered five days a week over 7.8 weeks or 6,460 cGy in 19 fractions of 340 cGy delivered three days a week over 6.3 weeks. At a median follow-up of five years, there was no difference in relapse-free survival rates between treatment arms.[26]

The RCTs comparing moderately hypofractionated and conventionally fractionated EBRT varied substantially in the risk group distribution of patients enrolled (Table 2). The RTOG 0415 trial enrolled exclusively low-risk patients,[28] the PROFIT trial enrolled only intermediate-risk patients,[27] and a smaller Italian trial reported by Arcangeli et al. was limited to high-risk patients.[33] All other trials enrolled patients from more than one risk group. While intermediate-risk patients constituted a majority of those included in the RCTs, high-risk patients represented a sizeable minority of nearly 20%. In absolute terms, more than 1,200 patients with high-risk disease were included across these trials.

The CHHiP trial and HYPRO trial presented analyses of the primary endpoint stratified by risk group. In CHHiP, the primary endpoint was time to biochemical or clinical failure. In the randomization comparing 6,000 cGy in 20 fractions of 300 cGy with 7,400 cGy in 37 fractions of 200 cGy, the hazard ratio for the primary endpoint was 1.17 (95% confidence interval [CI]: 0.67-2.02) in high-risk patients, 0.78 (95% CI, 0.62-0.98) in intermediate-risk patients, and 1.07 (95% CI: 0.48-3.39) in low-risk patients (with hazard ratios < 1 favoring the 6,000 cGy arm). The statistical test for an interaction between treatment effect and risk group was not significant ($P = 0.45$). In the randomization comparing 5,700 cGy in 300 cGy fractions with 7,400 cGy in 200 cGy fractions, there was similarly no evidence of a significant interaction between treatment effect and risk group ($P = 0.17$).[23]

In the HYPRO trial, the primary endpoint was relapse-free survival. The hazard ratios (again defined such that ratios < 1 favor the moderate hypofractionation arm) were 0.87 (95% CI: 0.63-1.22) in the high-risk subgroup and 0.85 (95% CI: 0.4-1.79) in the intermediate-risk subgroup with no statistical evidence of heterogeneity across subgroups ($P = 0.95$).[26]

Finally, the Italian trial, in contrast to other single institution studies, exclusively enrolled patients with high-risk disease and compared 8,000 cGy in 40 fractions of 200 cGy over 8 weeks versus 6,200 cGy in 20 fractions of 310 cGy over 5 weeks (four fractions per week). Results for the 168 patients accrued have now been reported at a median follow-up of nine years. The trial was not powered for cancer control. However, there was no significant difference in 10-year freedom from biochemical failure observed, with rates of 72% in the moderate hypofractionation arm and 65% in the conventional fractionation arm ($P = 0.15$).[33]

To date, there are limited published outcomes beyond five years for moderate hypofractionation. Therefore, current evidence supports similar *early* cancer control with this approach. Further, in the published reports to date, biochemical measures of cancer control predominate, and it is acknowledged that these are imperfect surrogates for more important longer-term oncologic outcomes including disease-specific and overall survival. Additional follow-up will be valuable in establishing the impact of these moderate hypofractionation regimens on long-term cancer control. The evidence is most robust for men with low-risk and intermediate-risk disease, as most men treated on these RCTs (over 5,000) fell in these categories. However, patients with high-risk disease are reasonably well represented in the completed trials and there is no clear evidence of heterogeneity of the treatment effect for moderately hypofractionated EBRT in high-risk patients compared to those with low- or intermediate-risk disease. The task force thus recommends that moderately hypofractionated EBRT be offered to patients across all risk groups after a discussion of risks and benefits.

It should be noted finally that, with the exception of a small subset of patients in the Fox Chase trial, the clinical target volume in the RCTs evaluating moderate hypofractionation did not include the pelvic lymph nodes; EBRT was instead delivered to the prostate gland with or without inclusion of the seminal vesicles. Recommendations for or against the use of elective pelvic nodal EBRT in patients with high-risk prostate cancer are beyond the scope of this guideline. For patients with high-risk localized prostate cancer, it is emphasized that the recommendations in this guideline regarding moderate hypofractionation apply to those scenarios where the decision has been made to include the prostate and seminal vesicles in the EBRT target volume but to exclude the pelvic lymph nodes. Prostate cancer control outcomes: Impact of patient age, comorbidity, anatomy, and urinary function

Statement KQ1D: In patients who are candidates for EBRT, moderate hypofractionation should be offered regardless of patient age, comorbidity, anatomy, or urinary function. However, physicians

should discuss the limited follow-up beyond five years for most existing RCTs evaluating moderate hypofractionation.

- **Recommendation strength**: Strong
- **Quality of evidence**: High
- **Consensus**: 94%

The efficacy of moderately hypofractionated EBRT does not appear to be impacted by patient age, comorbidity, or anatomy. Baseline characteristics were well-balanced in the arms of all the large prospective RCTs comparing moderately hypofractionated and conventionally fractionated EBRT. Eligibility criteria based on age, comorbidity, and anatomy were generally similar between the trials. Most of the trials excluded patients with previous pelvic EBRT or other treatment for prostate cancer (other than biopsy or transurethral resection of the prostate [TURP]), as well as those with another active malignancy in the past 5 years (except localized basal or squamous cell skin carcinoma).

In the CHHiP trial, the median age was 69 years (range 44-85 years). Men with World Health Organization (WHO) performance status of 0 or 1 were eligible. Additional exclusion criteria included life expectancy of $<$ 10 years, comorbid conditions precluding radical EBRT, bilateral hip prosthesis, and full anticoagulation treatment (criterion removed July 1, 2009). Of note, 11% of participants had diabetes, 40% hypertension, 4% inflammatory bowel disease, 8% previous pelvic surgery, 7% symptomatic hemorrhoids, and 8% prior TURP. In prespecified subgroup analyses, older men (age $>$ 69 years) had a reduced biochemical or clinical failure rate with 6,000 cGy in 300 cGy fractions compared to 7,400 cGy in 200 cGy fractions (Hazard ratio [HR] 0.59; 90% CI: 0.43-0.81), but younger men (age $\leq$ 69 years) showed no difference between treatment groups (HR 1.11; 90% CI: 0.84-1.48) (test for interaction, $P = 0.01$). This difference was not seen for the 5,700 cGy group ($P = 0.73$).[15]

In the Dutch HYPRO trial, median age was 70 years (range 44-85 years; interquartile range [IQR]: 66-75 years). Men with WHO performance status of 0 to 2 were eligible. Forty-five percent of participants had a prostate volume $\leq$ 50 cm^3 and 51% had a volume $>$ 50 cm^3 (4% unknown). In post-hoc multivariate analyses, age ($>$ 70 vs $\leq$ 70 years, multivariate HR 0.89, 95% CI: 0.64-1.22, $P = 0.46$) and prostate volume ($<$ 50 cm^3 vs $\leq$ 50 cm^3, multivariate HR 1.15, 95% CI: 0.82-1.61, $P = 0.42$) were not associated with relapse-free survival outcome. Post-hoc analyses of relapse-free survival showed no interaction effect between treatment group and any analyzed subgroup (including age and prostate volume), all having comparable survival.[18]

In the PROFIT trial, the median age was 71 years (IQR: 67-75 years). Additional exclusion criteria included radiation treatment plan not meeting dose constraints for the hypofractionation arm of the trial and inflammatory bowel disease. Eleven percent had a history of myocardial infarction, 57% hypertension requiring medication, 17% diabetes, 3% bowel disorders, and 2% bladder disorders. In addition, 56% of patients had a cardiac history and 11% a respiratory history within the past 5 years.[27]

In RTOG 0415, the median age was 67 years, with 38.5% who were $\geq$ 70 years and 16.7% who were $\leq$ 59 years. Eligibility criteria included Zubrod performance status $<$ 2. Over 92% of participants had no physical limitations (Zubrod performance score 0).[17]

Finally, it should be noted that measures of baseline urinary function were relatively sparsely reported across the large-scale RCTs. No trials provided analyses of the efficacy of moderately hypofractionated EBRT stratified by baseline urinary function.

In summary, the reported trials were generally representative of the prostate cancer patient population and there does not appear to be a consistent effect of age, comorbidity, or anatomy on the efficacy of moderately hypofractionated EBRT that would preclude its use. However, given limited published outcomes beyond five years for most existing RCTs evaluating moderate hypofractionation, additional follow-up and analyses will be valuable.

Toxicity and quality of life.

Statement KQ1E: Men should be counseled about the small increased risk of acute gastrointestinal (GI) toxicity with moderate hypofractionation. Moderately hypofractionated EBRT has a similar risk of acute and late genitourinary (GU) and late GI toxicity compared to conventionally fractionated EBRT. However, physicians should discuss the limited follow-up beyond five years for most existing RCTs evaluating moderate hypofractionation.

- **Recommendation strength**: Strong
- **Quality of evidence**: High
- **Consensus**: 100%

Multiple phase III RCTs and meta-analyses have compared acute toxicity for moderate hypofractionation versus conventional fractionation. These studies are consistent in showing similar acute GU toxicity in both treatment arms (up to 90-120 days post-RT), with rates of grade $\geq$2 acute GU toxicity of approximately 30-60% and grade $\geq$ 3 as high as 20% (Table 2). However, hypofractionation is associated with a greater risk of acute moderate GI toxicity. CHHiP, PROFIT, HYPRO and Fox Chase all found increased risk of acute GI toxicity with hypofractionation[23,25,27,29] and the Italian trial noted a non-significant trend.[34] Aluwini et al., found that grade $\geq$ 2 GI toxicity up to 120 days post-RT in the HYPRO trial was more common with hypofractionation (42% versus 31%, odds ratio [OR] 1.6, 95% CI: 1.19-2.14). Grade $\geq$ 3 toxicity was uncommon (~ 6%) and was similar between hypofractionated and conventional fractionation. In addition, acute radiation side effects occurred earlier in time (4 to 5 weeks) for moderate hypofractionation than with conventional fractionation.[25] It should be noted that in the CHHiP trial, while peak acute GI toxicity was greater in the moderately hypofractionated arms in early weeks, there was no difference in the prevalence of grade $\geq$ 2 GI toxicity between the arms by 18 weeks after the start of EBRT.[23]

The same RCTs show that moderately hypofractionated EBRT has similar risk of late genitourinary and late gastrointestinal toxicity compared to conventionally fractionated EBRT, with the caveat that all but one of these trials has been reported with median follow-up of 5-6 years. (Nine-year follow-up has been reported in the relatively small Italian trial.[33]) Late toxicity results from the RCTs must be considered with the trial design in mind. Some trials were designed to be isoequivalent in biological dose for prostate and late effects, while others delivered a higher effective dose in the hypofractionated arm (Table 2). The trials with similar biologically effective doses in the conventional and hypofractionated arms included over 4,000 patients and all found no statistical difference in clinician-reported late urinary or gastrointestinal toxicity or patient-reported GU or GI symptoms.[23,27,33]

Two of the RCTs—HYPRO and RTOG 0415—did identify a somewhat increased risk of late toxicity.[24,28] HYPRO was

designed as a superiority trial for its primary endpoint of relapse-free survival and the moderately hypofractionated arm had an escalated biologically effective dose compared to the conventional fractionation arm. Late toxicity was compared separately according to a predetermined non-inferiority criterion. Grade ≥2 GI toxicity at three years was 18% in the conventional arm versus 22% in the moderately hypofractionated arm, a small difference but one that exceeded the non-inferiority definition of no more than 2.8% increased risk. Interestingly, HYPRO also noted that the conventional fractionation arm was associated with greater high-grade GU toxicity at three years (grade ≥ 3 GU: 19% vs 13%).[24] These results should be interpreted in the context of the dose escalation employed in the moderately hypofractionated arm and the relatively large target volume that included the gland and seminal vesicles in a large majority of enrolled patients. RTOG 0415 also found increased frequency of maximum late grade 2 GI toxicity (risk ratio [RR] 1.59) and GU toxicity (RR 1.31) with hypofractionation but was designed with a higher effective dose for normal tissues in the hypofractionated arm.[28]

Taken together, the results from the phase III trials of conventional versus moderate hypofractionation do not show a consistent increase in late toxicity for moderate hypofractionation regimens. It should be further noted that the frequency of late toxicity observed in these trials was comparable to historical standards of dose-escalated conventional fractionation.

Some urinary symptoms may be more likely with hypofractionation. Arcangeli et al. have reported that, while overall late GU/GI toxicity rates were similar in the Italian RCTs, the hypofractionated arm had a significant increase in all grade late hematuria (17% versus 4%), although the events were predominantly grade 1 and no difference in actuarial grade ≥ 2 hematuria was found.[33] In addition, while overall late GU toxicities were comparable in the HYPRO trial, a review of individual items noted an association between hypofractionation and significant nocturia (> 6 times per night—OR 4.94, 95% CI: 1.87-13.09) and incontinence (OR 1.52, 95% CI: 1.03-2.24).[24] HYPRO also used a hypofractionated regimen of 6,460 cGy in 19 fractions of 340 cGy, a higher dose per fraction than other RCTs of moderate hypofractionation (Table 2).

To date, in none of the four completed large-scale multicenter RCTs have analyses of acute or late toxicity stratified by treatment arm been presented for subgroups of interest. Specifically, based on reports to date, it is unknown whether moderate hypofractionation might have *excess* acute or late toxicity compared to conventional hypofractionation in, for example, elderly patients, those with larger gland volumes, or those with significant baseline voiding dysfunction. Multivariable regression analyses have been completed in a few trials to assess the association between baseline characteristics and acute and late toxicity following moderate hypofractionation. In the HYPRO trial, for example, men with urinary and bowel symptoms at baseline (grade ≥ 2 on the RTOG scale) were significantly more likely to experience acute GU and GI toxicity following EBRT, whether moderately hypofractionated or conventional.[25] Late toxicity after moderate hypofractionation has similarly been found to be significantly associated with a number of factors, including baseline grade 2 GU/GI symptoms,[24,29] age,[24] and prostate gland volume.[24,32] It is emphasized, however, that these factors are not unique to hypofractionation as they have all similarly been found to be associated with a greater late toxicity risk after conventional fractionation. Fox Chase investigators found that a baseline International Prostate Symptom Score (IPSS) score of 12 or more was associated with increased risk of late GU toxicity following moderate hypofractionation ($P = 0.003$),[29] but baseline IPSS score was not associated with risk of late GU toxicity in the MD Anderson trial.[32] Secondary analyses of the completed large-scale trials addressing toxicity in these and other subgroups of interest would be valuable in identifying any patient groups likely to experience *differential* toxicity with moderate hypofractionation compared to conventional fractionation, but to date no such groups have been identified.

In addition to clinician-reported toxicity, patient-reported outcomes (PROs) were included in a number of the RCTs and these provide measures of quality of life (QOL).[35] The largest report of QOL comes from a sub-study of the CHHiP trial in which 2,100 patients participated. The sub-study's primary endpoint was overall bowel bother and this was assessed by QOL questionnaires incorporating a number of validated instruments prior to EBRT and at intervals thereafter up to 24 months following EBRT. Moderate bowel bother at 24 months was observed in 5%, 6%, and 5% of men in the 7,400 cGy, 6,000 cGy, and 5,700 cGy arms, respectively. Severe bowel bother at 24 months was seen in < 1% of each treatment arm. There were no significant differences observed between arms. Similarly, no significant differences across treatment regimens were seen in the secondary outcomes of urinary and sexual bother. Prostate-specific QOL results from RTOG 0415 have also been reported in abstract form.[36] The Expanded Prostate Index Composite (EPIC) questionnaire was administered at baseline, 6 months, and 12 months. Changes in scores compared to baseline were assessed in each of EPIC's four domains: bowel, urinary, sexual, and hormonal. At 6 months, there were no differences in change scores between the moderately hypofractionated and conventionally fractionated arms in any of the four domains. At 12 months, there was a larger decline in the bowel domain in patients treated with moderate hypofractionation, but this did not meet the pre-determined threshold for clinical significance. When considered together, PROs from these trials indicate that moderately and conventionally fractionated EBRT have similar—and modest overall—effects on QOL.

Key Question 2

In patients with localized prostate cancer who are candidates for EBRT, how do moderately hypofractionated EBRT regimens used in clinical trials compare in terms of prostate cancer control, toxicity, and quality of life and can particular regimens be recommended based on prostate cancer risk stratification group, age, comorbidity, anatomy (e.g. prostate gland volume), and baseline urinary function?

Statement KQ2A: Regimens of 6,000 cGy delivered in 20 fractions of 300 cGy and 7,000 cGy delivered in 28 fractions of 250 cGy are suggested since they are supported by the largest evidentiary base. One optimal regimen cannot be determined since most of the multiple fractionation schemes evaluated in clinical trials have not been compared head to head.

- **Recommendation strength**: Conditional
- **Quality of evidence**: Moderate
- **Consensus**: 100%

Statement KQ2B: One moderately hypofractionated regimen is not suggested over another for cancer control for specific risk groups and the efficacy of moderately hypofractionated EBRT regimens does not appear to be impacted by patient age, comorbidity, anatomy, or urinary function.

- **Recommendation strength**: Conditional
- **Quality of evidence**: Moderate
- **Consensus**: 100%

Multiple moderately hypofractionated radiation regimens have been evaluated in RCTs (Table 2). Modern trials using IMRT or other modulated treatment techniques, often with image guidance, consistently demonstrate similar early cancer control and generally indicate no difference in late GU and GI toxicity. However, the only study that directly compared hypofractionation regimens was the CHHiP trial, which found 5,700 cGy in 19 fractions of 300 cGy had inferior cancer control compared to 6,000 cGy in 20 fractions of 300 cGy. Therefore, the 6,000 cGy regimen is preferred over the 5,700 cGy regimen for cancer control.[23]

Among the dose-fractionation schemes that have been tested, the task force prefers 6,000 cGy delivered in 20 fractions of 300 cGy fractions over four weeks or 7,000 cGy in 28 fractions of 250 cGy over 5.6 weeks, as these regimens have been evaluated in the largest number of patients. The strongest evidence supports 6,000 cGy in 20 fractions of 300 cGy, since this regimen was used in two different RCTs, has been tested in all risk groups, and has been evaluated both in the presence and absence of androgen deprivation therapy. Of note, only low-risk patients were included in the RTOG 0415 trial that evaluated 7,000 cGy in 28 fractions over 5.6 weeks,[28] and thus this regimen has not been prospectively studied in a randomized fashion in intermediate- and high-risk patients. As the hypofractionated regimen employed in the HYPRO trial (6,460 cGy in 19 fractions of 340 cGy delivered three days a week over 6.3 weeks) was not shown to confer superior cancer control over the conventional regimen against which it was compared and yet was associated with significantly greater late grade $\geq$ 3 genitourinary toxicity, it is not a regimen preferred by the task force.[26]

Significant dose escalation beyond 6,000 cGy in 20-fraction regimens also appears to be associated with a risk of severe late GU and GI toxicity. In a single-institution cohort of 28 men with localized prostate cancer treated to 6600 cGy in 20 fractions of 330 cGy over 4.5 weeks, there were separate single events of late grade 4 GU and GI toxicity at a median follow-up of 108 months, suggesting a relatively narrow therapeutic window for moderately hypofractionated regimens in this dose range.[37]

Prostate cancer risk stratification group, patient age, comorbidity, anatomy, and urinary function

As discussed in KQ1C, the efficacy of moderately hypofractionated EBRT does not appear to be impacted by prostate cancer risk group. Significant differences in the presenting characteristics of the populations enrolled in the RCTs of moderate hypofractionation, endpoint definitions, the use of concomitant ADT, volumes, and other factors (Table 2) preclude any across-trial comparisons of the efficacy of the various regimens by risk group. However, it is noted that some moderate hypofractionation regimens have been more broadly studied across risk groups than others. Low-risk patients were included in the RTOG 0415 trial (7,000 cGy in 28 fractions of 250 cGy),[28] CHHiP trial (5,700 cGy in 19 fractions of 300 cGy and 6,000 cGy in 20 fractions of 300 cGy fractions),[23] and MD Anderson trial (7,200 cGy in 30 fractions of 240 cGy over 6 weeks).[32] Intermediate-risk patients were included in the CHHiP trial, PROFIT trial (6,000 cGy in 20 fractions of 300 cGy),[27] HYPRO trial (6,460 cGy in 19 fractions of 340 cGy delivered in three fractions per week),[26] Fox Chase trial (7,020 cGy in 26 fractions of 270 cGy over 5.2 weeks),[29] and MD Anderson trial. Finally, high-risk patients were studied in the CHHiP trial, HYPRO trial, Fox Chase trial, and Italian trial (6,200 cGy in 20 fractions of 310 cGy over 5 weeks).[33] Thus, the regimen best represented across all risk groups appears to be 6,000 cGy in 20 fractions over 4 weeks. In the absence of head-to-head randomized comparisons within specific risk groups, however, the task force cannot recommend one regimen over another for specific risk groups among those that have been studied.

Similarly, based on the completed trials, the efficacy of moderately hypofractionated EBRT regimens does not appear to be affected by patient age, comorbidity, or anatomy. Subgroup analyses of the CHHiP trial (which was not designed to directly compare its two hypofractionated schedules), suggested that older men (age $>$ 69 years) had a reduced biochemical or clinical failure rate with 6,000 cGy in 20 fractions of 300 cGy (but not with 5,700 cGy in 19 fractions of 300 cGy) when compared to 7,400 cGy in 37 fractions of 200 cGy fractions.[15] Aside from this, there does not appear to be a consistent effect of age, comorbidity, or anatomy on the efficacy of moderately hypofractionated EBRT (when compared to conventionally fractionated therapy) and it is therefore unlikely that there would be any significant differences between the various moderately hypofractionated schedules. However, in the absence of randomized comparisons between specific moderate hypofractionation regimens, no definitive conclusion can be drawn regarding their comparative efficacy as impacted by age, comorbidity, anatomy, or baseline urinary function. As discussed in section KQ1D above, certain patient factors (such as baseline GU/GI symptoms, age, and prostate size) have been associated with increased risk of toxicity after moderate hypofractionation – in the same way that these factors have been associated with increased toxicity with conventional fractionation – and these should be taken into consideration when considering the impact of specific regimens on side effects.

Key Question 3

In patients with localized prostate cancer who are candidates for EBRT, how does ultrahypofractionated EBRT ($\geq$ 500 cGy per fraction) compare to conventionally fractionated EBRT (180-200 cGy per fraction) in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ3A: In men with low-risk prostate cancer who decline active surveillance and choose active treatment with EBRT, ultrahypofractionation may be offered as an alternative to conventional fractionation.

- **Recommendation strength**: Conditional
- **Quality of evidence**: Moderate
- **Consensus**: 88%

Statement KQ3B: In men with intermediate-risk prostate cancer receiving EBRT, ultrahypofractionation may be offered as an alternative to conventional fractionation. The task force strongly

encourages that these patients be treated as part of a clinical trial or multi-institutional registry.

- **Strength of recommendation**: Conditional
- **Quality of evidence**: Low
- **Consensus**: 94%

Statement KQ3C: In men with high-risk prostate cancer receiving EBRT, the task force does not suggest offering ultrahypofractionation outside of a clinical trial or multi-institutional registry due to insufficient comparative evidence.

- **Strength of recommendation**: Conditional
- **Quality of evidence**: Low
- **Consensus**: 94%

To date, there are no published efficacy and toxicity data from RCTs comparing ultrahypofractionated and conventionally fractionated EBRT. Nonetheless, several prospective non-randomized studies have documented the safe delivery of ultrahypofractionation for patients with localized prostate cancer[38-52] and these results appear to apply to patients with prostate volumes up to 100 cm^3 and with mild to moderate urinary symptoms at baseline (IPSS $<$ 20). Table 3 lists the prospective studies with a median follow-up of greater than 48 months. Good biochemical control and low toxicities are seen but it is noteworthy that there are very few published data beyond five years for any risk group (77% of the cohorts reported low-risk disease; almost none reported high-risk disease). Since ultrahypofractionation is a non-invasive treatment (like other external beam techniques), there are relatively few restrictions on patient age or comorbidity.

During the literature search period for this guideline, there was data comparing conventionally fractionated and ultrahypofractionated EBRT regimens ($\geq$ 500 cGy per fraction) from one cohort study,[53] one propensity-matched analysis,[54] and one abstract.[55] Data regarding efficacy were available from two of these datasets, both of which included exclusively low-risk patients. No prospective studies comparing ultrahypofractionated and conventionally fractionated EBRT in intermediate- and high-risk prostate cancer with published efficacy data were identified. Musunuru et al. reported outcomes for 582 patients with low-risk prostate cancer treated between 2006 and 2008 (matched for risk and treatment era). Patients were managed with active surveillance (AS, n = 181), radical prostatectomy (RP, n = 59), conventional EBRT (7,600 cGy in 38 fractions of 200 cGy over 7.5 weeks, n = 66), low-dose-rate (LDR) brachytherapy with iodine-125 (14,500 cGy, n = 192), or ultrahypofractionation (3,500 cGy in 5 fractions of 700 cGy over 5 weeks, n = 84). Median follow-up was 73 months. The 6-year biochemical disease-free survival rates for conventional EBRT and ultrahypofractionation were 92.1% and 95.8%, respectively (*P* value between conventional EBRT and ultrahypofractionation not reported).[56]

Loblaw et al. reported propensity-matched analyses of ultrahypofractionation, LDR, and conventional fractionation for patients in a multi-institutional Canadian database (PROCARS). In this study, 602 low-risk patients were compared pre-match: ultrahypofractionation (3,500 cGy in 5 fractions of 700 cGy over 5 weeks, n = 80), LDR brachytherapy with iodine-125 (14,400-14,500 cGy, n = 458), and conventional fractionation (7,400-7,980 cGy in 37-42 fractions over 7.5-8.5 weeks, n = 64). Median follow-up was 61, 68, and 86 months, respectively. For the conventional and ultrahypofractionation patients, a biochemical disease-free survival (bDFS) trend was seen favoring ultrahypofractionation prior to matching ($P = 0.08$), which achieved significance following matching ($P < 0.001$). At six years, bDFS was 85.9% for conventional fractionation and 100.0% for ultrahypofractionation for the matched patients ($P = 0.045$).[54]

For toxicity, comparative data were available from two studies. Widmark et al. reported early results from the HYPO-RT-PC trial in abstract form at ASTRO 2016.[55] An updated toxicity analysis, along with efficacy data, was subsequently presented at ESTRO 2018 but falls outside the literature review period for this guideline. In this trial, 1,200 intermediate or high-risk patients were randomized to 7,800 cGy in 39 fractions of 200 cGy over 8 weeks versus 4,270 cGy in 7 fractions of 610 cGy over 2.5 weeks. No ADT was used and 80% of patients were treated with 3-D CRT and the remaining 20% with volumetric modulated arc therapy. Results were reported at a median follow-up of 52 months (866 patients had a minimum of two years of follow-up) and Table 4 summarizes the toxicity and quality of life differences. There was worse acute bowel toxicity, which normalized at 3 months, and worse urinary

Table 3. Studies of Outcomes for Patients with Early-Stage Prostate Cancer Treated With SBRT With Minimum Median Follow-Up 48 Months (KQ3)

Trial	N	Median Follow-Up	Dose	EQD2	Gleason 6	5-Year bDFS	Acute G3+		Late G3+		
							GU	*GI*	*GU*	*GI*	*ED*
Pham, 2010[105] (abstract only)	40	5 years	3,400 cGy in 5 fx over 1 week	8,200 cGy	100%	93%	2%	0%	3%	0%	50%
Kupelian, 2013[106] (abstract only)	135	5 years	3,500-4,000 cGy in 4-5 fx over 1-2 weeks	8,650-11,060 cGy	80%	97%	NR	NR	NR	NR	NR
Mantz, 2014[72]	102	> 5 years	4,000 cGy in 5 fx in 2 weeks	11,060 cGy	69%	100%	2%	0%	NR	0%	NR
Hannan, 2016[45]	91	4.5 years	4,500-5,000 cGy in 5 fx over 1 week	13,800-16,800 cGy	47%	99%	0%	2%	5%	7%	26%
Musunuru, 2016[53]	84	6.2 years	3,500 cGy in 5 fx over 4 weeks	8,650 cGy	100%	97%	1%	0%	0%	1%	43%
Zimmerman, 2016[75]	80	6.9 years	4,500 cGy in 9 fx over 9 weeks	8,470 cGy	100%	96%	NR	NR	4%	13%	NR
Total†	532				80%	98%	1.2%	0.6%	3%	2.6%	37%

bDFS: Biochemical disease-free survival; ED: Erectile dysfunction; EQD2: Equivalent dose in 2-Gy fractions; Fx: Fraction; GI: Gastrointestinal; GU: Genitourinary; int.: Intermediate; NR = not reported
†Weighted average

Table 4. Toxicity and Quality of Life From the 2016 Presentation of HYPO-RT-PC RCT (KQ3)[55]

Outcome	UHF	CF	*P* Value
Acute grade 2+ urinary toxicity	27.6%	22.8%	0.11
Acute grade 2+ GI toxicity	9.4%	5.3%	0.23
2-year grade 2+ urinary toxicity	5.4%	4.6%	0.59
2-year grade 2+ GI toxicity	2.2%	3.7%	0.20
2-year impotence (16% at baseline)	34%	34%	
QOL (PRO) at 2 years	No difference		
Acute bowel QOL	Worse at < 3 months (but same at 3 months)		Not reported
1-year urinary QOL	Worse for UHF		Not reported
Sexual QOL	Same		

CF = conventionally fractionated; PRO = patient-reported outcome; QOL = quality of life; UHF = ultrahypofractionated

function at one year for the ultrahypofractionated arm. However, there were no differences in overall QOL, sexual function, or grade $\geq$ 2 toxicities. In the Musunuru paper, there was higher grade $\geq$ 2 dysuria, greater need for TURP, and a trend towards higher use of argon plasma coagulation for radiation proctitis in patients receiving conventionally fractionated EBRT (compared to those receiving ultrahypofractionation).[56]

Key Question 4

In patients with localized prostate cancer who are candidates for EBRT, how do ultrahypofractionated EBRT regimens used in clinical trials compare in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ4A: Ultrahypofractionated prostate EBRT of 3,500 to 3,625 cGy in 5 fractions of 700 to 725 cGy to the planning target volume may be offered to low- and intermediate-risk patients with prostate sizes less than 100 cm^3. The key dose constraints in KQ5B should be followed.

- **Recommendation strength**: Conditional
- **Quality of evidence**: Moderate
- **Consensus**: 88%

Statement KQ4B: Five-fraction prostate ultrahypofractionation at doses above 3,625 cGy to the planning target volume is not suggested outside the setting of a clinical trial or multi-institutional registry due to risk of late toxicity.

- **Strength of recommendation**: Conditional
- **Quality of evidence**: Moderate
- **Consensus**: 100%

Statement KQ4C: Five-fraction prostate ultrahypofractionation using consecutive daily treatments is not suggested due to potential increased risk of late urinary and rectal toxicity.

- **Strength of recommendation**: Conditional
- **Quality of evidence**: Very Low
- **Consensus**: 100%

There is an absence of phase III data comparing differing dose and fractionation schemes for prostate ultrahypofractionation. Prostate cancer control, toxicity and quality of life outcomes have been analyzed using a variety of dose and fractionation schemes. The largest number of prostate ultrahypofractionation patients in the literature were treated with 3,500 cGy in 5 fractions of 700 cGy or 3,625 cGy in 5 fractions of 725 cGy and these regimens were well tolerated and achieved acceptable biochemical control rates. There was relatively sparse reporting of the details of dose specification and dose heterogeneity. Most studies documented the intended dose to the planning target volume (PTV) while in others dose was prescribed to the clinical target volume (CTV); almost none documented what was considered a minor or major deviation in achieving the prescribed doses or how many patients received a non-deviated plan. There was also insufficient evidence to compare the impact of age, comorbidity, or urinary function on biochemical control, toxicity, or quality of life among differing schemes of prostate ultrahypofractionation.

In 2016, Katz et al. reported on 515 patients (63% low, 30% intermediate, and 7% high-risk by National Comprehensive Cancer Network [NCCN] risk category) treated with prostate ultrahypofractionation to 3,500 or 3,625 cGy in 5 fractions of 700 or 725 cGy over 5 days with median follow-up of 84 months. Eight-year bDFS rates were 93.6%, 84.3%, and 65.0% for NCCN low-, intermediate-, and high-risk patients ($P < 0.0001$). When intermediate-risk patients were subdivided into favorable and unfavorable subsets (unfavorable was defined as a Gleason score of 4+3=7 or more than 1 intermediate-risk factor of cT2b, prostate-specific antigen (PSA) 10 to 20, and Gleason score of 3+4=7), seven-year bDFS rates were 93.2% for favorable intermediate-risk and 68.2% for unfavorable intermediate-risk. Comparing bDFS rates for low and favorable intermediate-risk patients, 9-year biochemical disease-free survival rates were 95.3% and 93.5% for patients treated to 3,500 cGy versus 3,625 cGy ($P = 0.67$).[47]

Similarly, an earlier article by the same authors reported comparable rates of acute RTOG grade 1 and 2 GU and rectal toxicity for 5-fraction prostate ultrahypofractionation regimens of 3,500 cGy compared with 3,625 cGy. Among patients with a minimum follow-up of 12 months, no grade 3 acute toxicity was reported. Late grade 1, 2 and 3 GU toxicity was reported in 4%, 2% and 0% for patients treated to 3,500 cGy compared to 4.8%, 5.8%, and 0.5% for patients treated to 3,625 cGy. Late grade 1 and 2 rectal toxicity was noted in 4.2% and 0% of patients treated to 3,500 cGy compared with 5.3% and 2.9% of patients treated to 3,625 cGy.[57]

In considering the influence of patient characteristics on toxicity, Glowaki et al. reported on 132 patients treated with 3,500 cGy in 5 fractions of 725 cGy over 10 days, 13% of whom had diabetes, and found that the risk of grade $\geq$ 2 acute GU toxicity was 10% for men without diabetes compared with 29% of men with diabetes ($P = 0.04$).[58] Gomez et al. reported on 75 patients treated with a regimen of 4,000 cGy in 5 fractions of 800 cGy with median prostate volume of 103 cm^3 and found a strong and significant

decline in urinary QOL up to 12 months after treatment, along with a significant but modest decline in bowel QOL associated with large prostate volume.[59]

In contrast to the data for fractionation schemes using 3,500 to 3,625 cGy in 5 fractions of 700 to 725 cGy, five-fraction regimens with doses above 3,625 cGy are not recommended by the task force except as part of a clinical trial or multi-institutional registry. Hannan et al. reported a multi-institutional study that included 44 patients treated in a phase I dose escalation protocol starting at 4,500 cGy in 5 fractions of 900 cGy over 5 days, increasing to 4,750 cGy in 5 fractions of 950 cGy and, eventually, 5,000 cGy in 5 fractions of 1000 cGy, with an additional 47 patients then treated in a phase II study at 5,000 cGy in 5 fractions of 1000 cGy. In total, 36.3% of patients were NCCN low-risk, while 63.7% were NCCN intermediate-risk. Five-year freedom from biochemical failure rates (Phoenix definition) were 98.6% overall, 90.6% for 4,500 cGy, 100% for 4,750 cGy, and 100% for 5,000 cGy. By risk group, it was 100% for low-risk patients and 98% for intermediate-risk patients at 54 months median follow-up. No acute grade 3 or 4 GU toxicity was identified at any dose level, but there was a 1.6% incidence of acute grade 3 GI toxicity at 5,000 cGy. There was no late grade 3 or 4 toxicity at the 4,500 cGy level, but late grade 3 GU toxicity was identified at 4,750 cGy (6.7% grade 3) and 5,000 cGy (4.9% grade 3 and 1.6% grade 4). Late GI toxicity was identified as well at the 5,000 cGy level (6.6% grade 3 and 3.3% grade 4).[45]

Musunuru et al. also reported a dose escalation study comparing outcomes among 84 low-risk patients treated with 3,500 cGy in 5 fractions of 700 cGy over 5 weeks and 30 patients (60% low-risk and 40% intermediate-risk) treated with 4,000 cGy in 5 fractions of 800 cGy over 5 weeks. Two-, four- and six-year bDFS rates were 100%, 98.7% and 95.9% for 3,500 cGy (median follow-up 74 months) and 100%, 100% and not available for 4,000 cGy (median follow-up 36 months). There was no significant difference in incidence of acute GU or GI toxicity between 3,500 cGy and 4,000 cGy levels (Common Terminology Criteria for Adverse Events [CTCAE] version 3.0). There was, however, a significant increase in late toxicity observed at the 4,000 cGy level. Specifically, maximum late grade $\geq$ 2 GI toxicity was identified in 8% at 3,500 cGy compared with 20% at 4,000 cGy ($P = 0.012$), while maximum late grade $\geq$ 2 GU toxicity was seen in 5% at 3,500 cGy and 13% at 4,000 cGy ($P = 0.02$) (RTOG scale).[53]

In addition, Quon et al. reported minimally clinically important change (MCIC) in average urinary quality of life (EPIC questionnaire) among 19.5% of patients treated to 3,500 cGy and 24.1% treated to 4,000 cGy ($P = 0.6$). MCIC rates for average bowel QOL were 26.8% for 3,500 cGy and 41.4% for 4,000 cGy ($P = 0.16$).[60]

Taken together, these data have led the task force to conclude that doses $>$ 3,625 cGy in 5 fractions carry an increased risk of late toxicity and discourage the use of these regimens outside of clinical trials or multi-institutional registries.

Few data directly address treatment schedule or overall duration of treatment. A wide range of schedules have been employed across the prospective trials of ultrahypofractionated EBRT, including daily treatment, alternate-daily treatment, and weekly treatment. In an exploratory analysis of a phase 2 trial, King et al. compared the patient-reported urinary and rectal quality of life (using the EPIC instrument) between 21 patients treated with a daily schedule and 20 subsequent patients treated with an alternate-daily schedule. Despite the small size of the cohort, a significantly greater proportion of patients receiving daily treatment reported a "moderate" or "big problem" with respect to any rectal QOL item compared to those receiving alternate-daily treatment (38% vs. 0%, $P = 0.0035$).[61] Although this study did not meet the inclusion criteria of this literature review, it has influenced subsequent clinical trial design and leads the task force to conclude that it is prudent to avoid consecutive daily treatments when treating prostate cancer with ultrahypofractionation.

Key Question 5

In patients with localized prostate cancer who are receiving moderately hypofractionated or ultrahypofractionated EBRT, how do normal tissue constraints used in clinical trials compare in terms of toxicity and quality of life?

Statement KQ5A: At least two dose-volume constraint points for rectum and bladder should be used for moderately or ultrahypofractionated EBRT: one at the high-dose end (near the total dose prescribed) and one in the mid-dose range (near the midpoint of the total dose).

- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate
- **Consensus**: 100%

Statement KQ5B: Use of normal tissue constraints for moderately or ultrahypofractionated EBRT that differ from those of a published reference study is not recommended due to the risk of both acute and late toxicity.

- **Strength of recommendation**: Strong
- **Quality of evidence**: Low
- **Consensus**: 100%

Moderate hypofractionation is associated with both acute and late toxicity that is similar in severity to conventional fractionation when appropriate normal tissue dose-volume histogram (DVH) constraints are used. There have been several prospective RCTs looking at the safety and efficacy of moderate hypofractionation compared to conventional fractionation.[23,28,29,31,33,62-64] Each of these trials reported acute and/or late GI and GU toxicity. Although acute toxicity occurs earlier with moderate hypofractionation, as documented in these trials, it also subsides earlier. Each trial also reported the use of dose constraints for bladder and rectum. In general, these dose constraints limited dose at the high dose region (near the total prescribed dose) and at a mid-range level. For the trials using fractionation of 240 to 340 cGy, the dose constraints for rectum are shown in Figure 1A and bladder in Figure 1B.[23,28,29,31,62-65] The fractionation and dose constraints for these trials are also shown in Table 5.

Patient-reported QOL was also reported for several of the RCTs and no statistically significant differences were observed.[28,30,31,36,63] With the exception of RTOG 0415,[28] none of the studies with a non-inferiority design observed a significant difference in either physician-reported GI or GU late toxicity with moderate hypofractionation compared to conventional fractionation. While it is reassuring that patient-reported GI and GU QOL were similar in RTOG 0415, the difference in physician-reported late GI and GU toxicity may be explained by the normal tissue dose constraints

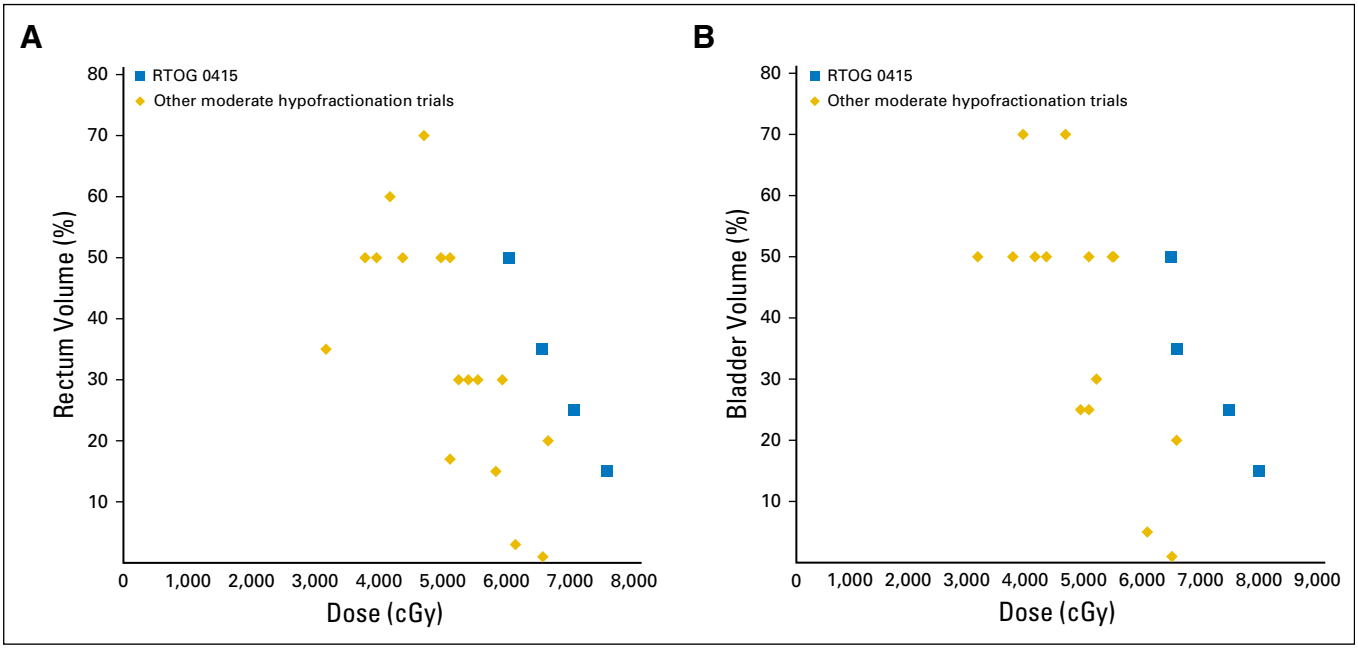

Fig 1. (A) Rectal dose constraints from trials of moderate hypofractionation. (B) Bladder dose constraints from trials of moderate hypofractionation.

used.[28,36] As shown in Figures 1A and 1B, the constraints used in RTOG 0415 were the least restrictive and may explain the difference in physician-reported toxicity observed.

Therefore, it is recommended when using moderate hypofractionation that one should use a combination of normal tissue volumes and dose constraints that are similar to, if not directly adapted from, one of the RCTs and preferably more restrictive than those used in RTOG 0415. Figure 2 illustrates the need for consistency in adopting normal tissue volumes and dose constraints as a combination to avoid unexpected toxicity. One should proceed with caution if a combination of normal tissue volumes and dose constraints other than those from a published reference study are used. To facilitate the meeting of rectal and bladder dose-volume

Table 5. Fractionation and Dose Constraints for Trials of Moderate Hypofractionation (KQ5)

			Bladder Constraints		Rectal Constraints	
Trial	Total Dose	Fraction Size	Dose	<Vol%	Dose	<Vol%
Italian[65]	6,200 cGy	310 cGy	5,425 cGy	50%	5,425 cGy	30%
			3,875 cGy	70%	3,875 cGy	50%
PROFIT[27]*	6,000 cGy	300 cGy	3,700 cGy	50%	3,700 cGy	50%
			4,600 cGy	70%	4,600 cGy	70%
CHHiP[23]	6,000 cGy	300 cGy	6,000 cGy	5%	6,000 cGy	3%
			4,860 cGy	25%	5,700 cGy	15%
			4,080 cGy	50%	5,280 cGy	30%
					4,860 cGy	50%
					4,080 cGy	60%
MD Anderson[31]	7,200 cGy	240 cGy	6,500 cGy	20%	6,500 cGy	20%
RTOG 0415[28]	7,000 cGy	250 cGy	7,900 cGy	15%	7,400 cGy	15%
			7,400 cGy	25%	6,900 cGy	25%
			6,900 cGy	35%	6,400 cGy	35%
			6,400 cGy	50%	5,900 cGy	50%
Norkus, 2009[62]	5,700 cGy	17 fx of 300 cGy + 3 fx of 450 cGy	5,130 cGy	30%	5,130 cGy	30%
			4,275 cGy	50%	4,275 cGy	50%
Norkus, 2013[63]	6,300 cGy	315 cGy	6,420 cGy	1%	6,420 cGy	1%
			5,000 cGy	50%	5,800 cGy	30%
					5,000 cGy	50%
Fox Chase[29]	7,020 cGy	270 cGy	5,000 cGy	25%	5,000 cGy	17%
			3,100 cGy	50%	3,100 cGy	35%
Sanguineti[64]	6,200 cGy	310 cGy	5,400 cGy	50%	Not reported	

Fx = fraction
*In the PROFIT trial, dose-volume criteria were based on rectal and bladder wall contours. In all remaining trials, dose-volume criteria were based on solid organ contours.

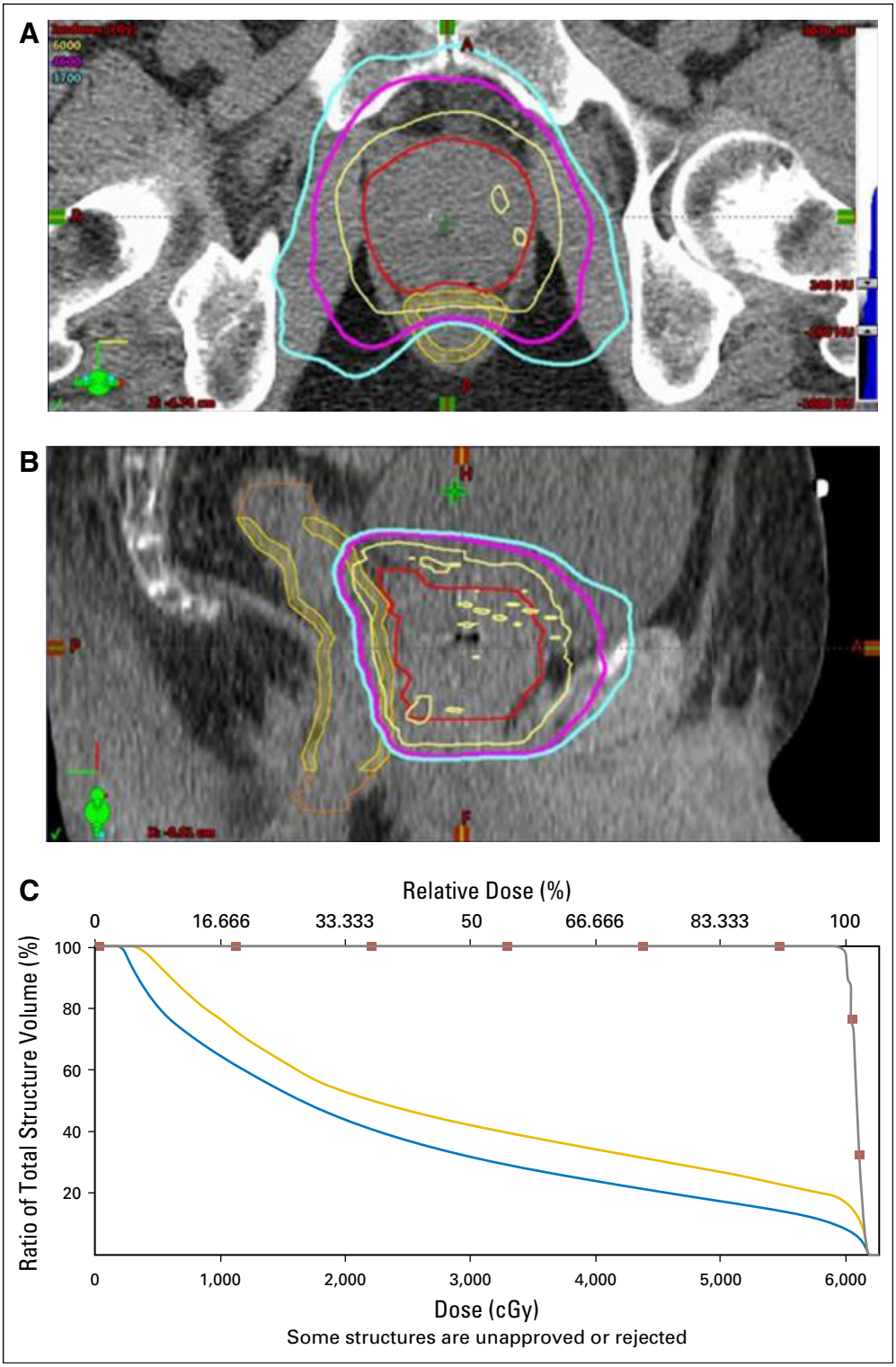

Fig 2. Examples of two methods of rectal contouring. The attached example prescribed to 6,000 cGy in 20 fractions compares the two methods of contouring the rectum in (A) the axial plane, (B) sagittal plane, and (C) representative DVH. The rectal sparing appears to be much greater using the CHHiP/RTOG 0415 method (orange) compared to the PROFIT method (yellow). If the CHHiP/RTOG 0415 contouring method were used with the PROFIT constraints, the rectum may be allowed to receive a greater dose than allowed on the PROFIT trial.

constraints and achieve consistency in daily treatment, a number of strategies have been developed and use of one or more of these is suggested: protocols to ensure that the bladder is comfortably full at time of treatment, prostate-rectal spacers to allow rectal dose sparing, and rectal balloon devices to assist in prostate immobilization.[66-69]

Ultrahypofractionation has both acute and late toxicity. Given limited RCTs to date to compare toxicity with conventional fractionation, there is insufficient data to recommend specific normal tissue constraints. There have been multiple reports of ultrahypofractionation for localized prostate cancer.[38,41,44,45,47,48,53,60,70-75] The majority of these trials have

centered exclusively on low-risk patients. There are no published RCTs comparing ultrahypofractionation versus conventional fractionation. The vast majority of the reports have used a prescription dose of 3,500 to 3,625 cGy in 5 fractions of 700 to 725 cGy.[38,41,47,53,57,60,70,71,74] Dose-volume constraints for those trials for the rectum are plotted in Figure 3A and bladder in Figure 3B. Given the lack of data comparing physician-reported toxicity and patient-reported quality of life outcomes of ultrahypofractionation to conventional fractionation, there are no normal tissue constraints recommended as a practice standard. One should proceed with caution if a combination of normal tissue volumes and dose constraints other than those from a published reference study are used. Finally, the strategies discussed above to facilitate meeting normal tissue dose-volume constraints are also recommended in the context of ultrahypofractionation.

Key Question 6

In patients with localized prostate cancer who are receiving moderately hypofractionated or ultrahypofractionated EBRT, how do treatment volumes used in clinical trials compare in terms of prostate cancer control and toxicity?

Statement KQ6A: Use of target volume and associated margin definitions for hypofractionated EBRT that deviate from those of a published reference study is not recommended, especially for ultrahypofractionated regimens.

- **Recommendation strength**: Strong
- **Quality of evidence**: Low
- **Consensus**: 100%

Given substantial variation in target volume and margin definitions among reports of moderately hypofractionated or ultrahypofractionated EBRT, data is lacking to compare their impact on prostate cancer control and toxicity. There is considerable heterogeneity among the gross tumor volume (GTV), CTV, and PTV definitions in the reported literature. With regard to moderate hypofractionation, the primary target has included the prostate with or without a portion of the seminal vesicles on a risk-adapted basis. Among the CHHiP, PROFIT, and RTOG 0415 reports, the margin expansion for the PTV did not exceed 10 mm. The PTV margin at the rectal interface was generally smaller but not < 4 mm.

The ultrahypofractionation literature is comprised largely of prospective single-arm cohorts conducted in many cases in single institutions. The extent of reporting of the details of target volume definitions was more variable than in the RCTs of moderate hypofractionation and, where reported, there was notable heterogeneity in the volumes employed. Nonetheless, some general observations can be made. The most common strategy for CTV definition, employed in several single-institution cohorts, identified the CTV as the prostate alone in low-risk patients and the prostate plus a variable portion of the seminal vesicles in intermediate-risk patients.[41,57,70-72,74] High-risk patients were poorly represented in these cohorts. With respect to PTV definition, the most commonly reported approach employed an isotropic 5 mm expansion around the CTV with the exception of a 3 mm posterior expansion.[38,47,49,57-59,74,76] Thus, in general terms, somewhat narrower PTV margins have been employed in the published cohorts of ultrahypofractionation than in the published RCTs of moderate hypofractionation.

In addition to heterogeneity in target volume definition, the completed trials of moderate hypofractionation and published cohorts of ultrahypofractionation varied substantially in the risk-group distribution of included patients, prescribed radiation dose, use of concomitant ADT, dose-volume constraints employed in radiation planning, technique, and extent of follow-up. Observed differences in prostate cancer control and toxicity across these trials may thus be due to a combination of several of these factors rather than single factors in isolation. It was therefore not possible to ascribe differences in these outcomes to variability in target volume definitions alone. Accordingly, the task force is unable to provide definitive guidance on optimal target volume definitions but recommends that caution be exercised if approaches are used that diverge from those in the published reference studies included in this document.

Key Question 7

In patients with localized prostate cancer who are receiving moderately hypofractionated or ultrahypofractionated EBRT, how does treatment using IGRT compare to treatment not using IGRT in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ7A: IGRT is universally recommended when delivering moderately or ultrahypofractionated EBRT.

- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate
- **Consensus**: 100%

The vast majority of moderately hypofractionated and ultrahypofractionated EBRT reports have utilized IGRT.[23,29,40,77-82] The exceptions used larger target volumes and a non-IMRT technique. Therefore, IGRT is believed to be central to the safe and effective delivery of hypofractionated EBRT, whether moderately hypofractionated or ultrahypofractionated. With the utilization of IMRT to deliver highly conformal hypofractionated schedules for treatment of prostate cancer there is a greater concern for known inter- and intrafraction prostate motion due to variations in both patient set-up and changes in bladder and rectal distension.[83-86] The increased utilization of IGRT has allowed for correction of this motion through a multitude of techniques but, ultimately, through identification of the prostate position followed by adjustment in treatment position to account for variations.[4] Without accounting for these changes, there is a concern for increased treatment toxicity to normal tissue and reduced local control, particularly with the steep dose gradients in many IMRT plans. This must be weighed against the fact that IGRT can lead to increased resource utilization, additional procedures, increased radiation dose to the patient, and a risk of local infection or sepsis due to fiducial marker placement.

Clinical evaluations comparing the benefits on local control and/or reduced toxicity with IGRT have been mixed.[77-79] The CHHiP trial attempted to evaluate this question by including a Phase 2 sub-study randomizing patients to IGRT or no IGRT.[23] At two years, there was no significant difference in grade 2 bowel or bladder toxicity in patients treated with or without IGRT.[87] Even without significant randomized evidence, there is a much larger volume of data regarding the safe and effective treatment of

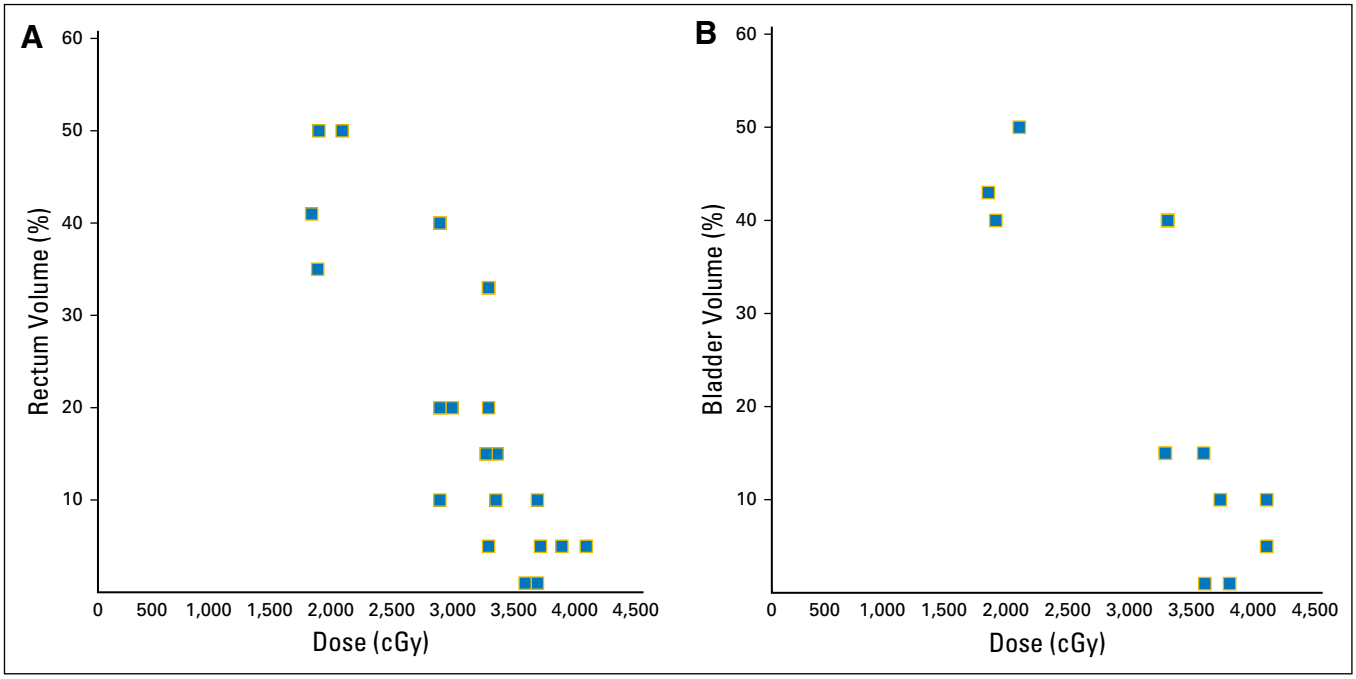

Fig 3. (A) Rectal dose constraints from trials of ultrahypofractionation. (B) Bladder dose constraints from trials of ultrahypofractionation.

prostate cancer with moderately and ultrahypofractionated regimens with IGRT.[29,40,80-82] These studies have outlined the favorable late toxicities and local control outcomes in treatment of these hypofractionated regimens. There is only limited evidence for safe and effective treatment with hypofractionated regimens in prostate cancer without IGRT, such as those by Lukka et al. or Yeoh et al.[88-90] These studies did not include ultrahypofractionated regimens, did not use IMRT, and employed lower doses and generally larger treatment volumes than utilized today. In view of this, the task force recommends the routine use of image guidance as a component of hypofractionated treatment regimens, and this is particularly the case where reduced PTV margins have been chosen.

While utilization of IGRT is recommended, there are many different modalities to evaluate prostate position (ultrasound [US], fiducial markers, cone beam computed tomography [CBCT]) and to track the position (4-dimensional and cine magnetic resonance imaging and radiofrequency transponder systems). Each system has its own advantages and disadvantages by comparing increased radiation dose, additional invasive procedures required, cost, accuracy, and time on the treatment table.[91-94] There are a number of studies comparing these technologies with respect to both outcomes and accuracy, yet the definitive benefit of one modality over another has not been identified.[93-97] Until randomized evidence regarding the benefit of these technologies is available, it is up to each institution to determine the appropriate modality for utilization of IGRT.

Key Question 8

In patients with localized prostate cancer who are receiving moderately hypofractionated or ultrahypofractionated EBRT, how does treatment using IMRT compare to treatment with 3-dimensional conformal radiation therapy (3-D CRT) in terms of prostate cancer control, toxicity, and quality of life?

Statement KQ8A: Non-modulated 3-D CRT techniques are not recommended when delivering moderately or ultrahypofractionated prostate EBRT.

- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate
- **Consensus**: 100%

There is insufficient evidence to evaluate prostate cancer control, toxicity, and quality of life with the use of non-modulated 3-D CRT treatment techniques for moderately hypofractionated EBRT. Studies demonstrating non-inferior prostate cancer control without a significant increase in late toxicity for moderately hypofractionated treatment schedules compared with conventionally fractionated treatment have predominantly used IMRT or other modulated treatment techniques. Evidence is also lacking to evaluate prostate cancer control, toxicity, and quality of life with the use of non-modulated 3-D CRT treatment techniques for ultrahypofractionated EBRT.

Many non-randomized studies employing conventionally fractionated treatment schedules were conducted in the 2000s comparing 3-D CRT and IMRT, showing reduced GI and GU toxicity with IMRT.[98-100] By 2010, IMRT techniques became the standard of care for conventionally fractionated prostate EBRT in the United States.[101] It is therefore not surprising that recent studies have largely utilized IMRT or other modulated treatment techniques.

The only RCT to directly compare 3-D CRT and IMRT for a hypofractionated treatment regimen was conducted in Brazil and used the same dose (7,000 cGy in 25 fractions of 280 cGy) and PTV margins (10 mm except posteriorly 7 mm).[3] A total of 215 patients were accrued, evenly divided between 3-D CRT and IMRT. With

Table 6. Large Scale Randomized Trials Evaluating Ultrahypofractionated EBRT in Localized Prostate Cancer

Trial	Planned accrual	Population	Primary Endpoint	Ultrahypofractionated Regimen	Comparator Regimen	Current Status
HEAT NCT01794403	456	LR and IR	Biochemical or clinical failure	3,625 cGy in 5 fractions	7,020 cGy in 26 fractions	Accruing
HYPO-RT-PC ISRCTN45905321	1,200	IR	Biochemical or clinical failure	4,270 cGy in 7 fractions	7,800 cGy in 39 fractions	Accrual complete
NRG-GU005	606	IR	HRQOL toxicity assessment	3,625 cGy in 5 fractions	7,000 cGy in 28 fractions	Accruing
PACE B NCT01584258	858	LR and IR (Gleason score ≤ 3+4)	Biochemical or clinical failure	3,625 cGy in 5 fractions	7,800 cGy in 39 fractions or 6,200 cGy in 20 fractions	Accrual complete

LR = low-risk; IR = intermediate-risk

a median follow-up of 56 months, the rate of RTOG grade ≥ 2 acute GI toxicity was 24% in the 3-D CRT arm and 7% in the IMRT arm ($P = 0.001$). The combined incidence of acute GI/GU toxicity was 28% in the 3-D CRT arm and 11% in the IMRT arm. The rate of RTOG grade ≥ 2 late GI toxicity was 21.7% in the 3-D CRT arm and 6.4% in the IMRT arm ($P = 0.001$) and the rate of grade ≥ 2 late GU toxicity was 12.3% in the 3-D CRT arm and 3.7% in the IMRT arm ($P = 0.02$). The 5-year biochemical control rate, defined as the PSA nadir plus 2 ng/mL according to the Phoenix Consensus Conference criteria, was 94.3% in the 3-D CRT arm and 95.4% in the IMRT arm (difference not statistically significant).[3]

The RCTs comparing moderately hypofractionated with conventionally fractionated EBRT in localized prostate cancer have utilized IMRT techniques either exclusively or predominantly but did not have randomization by technique (Table 2). The PROFIT trial allowed both 3-D CRT and IMRT techniques using consistent PTV margin expansions.[27] The RTOG 0415 trial likewise allowed both 3-D CRT and IMRT techniques, though only 21% of the 1115 patients accrued on the trial were treated using 3-D CRT techniques.[102] The CHHiP trial, in contrast, utilized IMRT techniques exclusively.[23] The HYPRO trial also only used IMRT techniques and 74% of the 820 patients were in the high-risk category.[26]

A single-institution study from Australia exclusively used 2-D and 3-D CRT treatment techniques with an isotropic 15 mm block margin around the prostate gland. With a median follow-up of 90 months, using patient-reported symptoms for GI and GU toxicity, 16-48% of patients reported an increase in at least one late GI symptom and 51% of patients reported an adverse effect on quality of life. In addition, 6% to 32% of patients reported an increase in at least one GU symptom and 48% reported an adverse effect on quality of life.[90] While not directly comparable to the RTOG toxicity criteria used by many other investigators, this study indicates a high prevalence of late GI and GU toxicity with uniform-beam-intensity treatment techniques and moderate to generous block margins.

For ultrahypofractionated treatment schedules, all but one published study used IMRT or other modulated techniques, including the studies by Musunuru, Katz, and King. The only ultrahypofractionated study to employ 3-D CRT treatment techniques used a dose-fractionation schedule of 4,500 cGy in 9 fractions of 500 cGy delivered once weekly over 9 weeks.[75] This differs from the dose-fractionation schedule used by all other investigators whose results have been published as of March 2017. The investigators also applied more generous PTV margins (10-15 mm except posteriorly 5-10 mm) than other published ultrahypofractionated studies. With a median follow-up of 83 months, the cumulative rate of RTOG grade ≥ 2 late GI toxicity was 30% and the cumulative rate of RTOG grade ≥ 2 late GU toxicity was 31.3%.[75]

Given the dearth of clinical trials using non-modulated 3-D CRT techniques for hypofractionated prostate EBRT, the strong evidence for lower GI and GU toxicity with IMRT compared to 3-D CRT techniques for conventionally fractionated prostate EBRT, and the Viani trial showing significant reductions in GI and GU toxicity with IMRT compared to 3-D CRT techniques for a hypofractionated treatment schedule, the use of non-modulated 3-D CRT techniques should be avoided when delivering moderately or ultrahypofractionated prostate EBRT. Most multi-institutional prospective trials using IMRT for planning and delivery of hypofractionated prostate EBRT have employed at least two dose-volume criteria for both bladder and rectum dose, including one criterion at the high dose end (near the total dose prescribed) and one in the mid dose range (near the midpoint of the total dose) as discussed in KQ 6. This represents a prudent approach and is recommended by the task force.

CONCLUSION

This evidence-based clinical practice guideline was developed to make recommendations on the use of hypofractionated EBRT in the treatment of localized prostate cancer. To reflect current practice patterns, a distinction was made between moderate hypofractionation (240-340 cGy per fraction) and ultrahypofractionation (≥ 500 cGy per fraction). Several large-scale RCTs comparing moderately hypofractionated and conventionally fractionated EBRT have been completed. These demonstrate that, compared to conventional fractionation, moderate hypofractionation confers similar prostate-cancer-control outcomes, similar rates of late toxicity, and only a slight excess in acute gastrointestinal toxicity. Moderate hypofractionation holds important advantages in terms of patient convenience and resource utilization. On the basis of this high-quality evidence, a strong agreement has been reached within the task force that moderately hypofractionated EBRT should be offered to patients choosing EBRT for the treatment of their prostate cancer. This recommendation holds across all risk groups. In patients who are deemed candidates for EBRT, the decision to offer moderate hypofractionation should not be affected by considerations of age, comorbidity, anatomy, or baseline urinary function.

While there is limited follow-up beyond 5 years in the completed trials, the existing evidentiary base nonetheless represents many thousands of patient-years of follow-up and many hundreds of recurrence and toxicity events. The task force has concluded that the accumulated data are thus sufficiently robust to justify routine use of moderate hypofractionation in clinical practice. While not directly comparable, it is worth noting that long-term follow-up beyond 5 years in RCTs comparing hypofractionated with conventionally fractionated EBRT in the adjuvant treatment of localized breast cancer did not identify any late-appearing differences in efficacy or toxicity.[103,104] Future updates to this guideline will take account of longer-term results from the completed trials of moderate hypofractionation. Finally, it should be noted that conventional fractionation, as it is supported by longer-term results and has similar efficacy with respect to cancer control outcomes, remains a reasonable—though somewhat less convenient and more costly—alternative to moderate hypofractionation in patients choosing EBRT.

The task force showed more uncertainty on the use of ultrahypofractionated EBRT. To date, the evidentiary base for ultrahypofractionation consists largely of prospective, single-arm trials conducted in low-risk and, to a lesser extent, intermediate-risk localized disease and with limited follow-up. There are no published efficacy data from randomized trials available at this time. However, data from the Scandinavian HYPO-RT-PC trial may form the basis to review and update the ultrahypofractionation recommendations in the near future. The recommendation for the use of ultrahypofractionated EBRT in low-risk localized prostate cancer has been graded by the task force as "conditional," reflecting only moderate-quality evidence and remaining uncertainty in the balance between benefit and risk associated with this treatment strategy. The recommendation for the use of ultrahypofractionated EBRT in intermediate-risk prostate cancer is also graded as "conditional," but as the evidentiary base is weaker than in low-risk disease, support of ongoing clinical trials and multi-institutional registries in this population is strongly encouraged. Given the paucity of highest quality evidence, the task force has conditionally recommended against the routine use of ultrahypofractionated radiation in high-risk localized prostate cancer. Finally, in view of the potential for harm, the task force has recommended conditionally against escalation in dose to the planning target volume beyond 3,625 cGy when 5-fraction regimens are used in routine practice outside of clinical trials or multi-institutional registries

When either moderately hypofractionated or ultrahypofractionated EBRT are undertaken, considerations around the technical aspects of treatment planning and delivery are important to ensure high-quality treatment. With any hypofractionated approach, the task force strongly recommends that IGRT be used and that non-modulated 3-D CRT techniques be avoided. While no specific recommendations regarding radiation target volumes and dose-volume criteria can be made, the task force advocates the general principle that, to confidently replicate the results of a published reference study, as far as possible the approach employed in that published study should be used. In the context of satisfactory EBRT planning and delivery parameters having been achieved, no specific radiation delivery platform is preferred over others.

The evidentiary base at present highlights the imperative within the radiation oncology community to support large-scale randomized clinical trials evaluating ultrahypofractionation. A number of such trials are underway or in design (Table 6). The conditional recommendations for ultrahypofractionation in low- and intermediate-risk prostate cancer should not be misinterpreted as obviating the need for such trials; indeed, the task force regards enrollment in prospective randomized clinical trials such as these as a preferred radiotherapeutic management approach in localized prostate cancer. Updates to this guideline will incorporate the toxicity and efficacy results from these trials as they emerge.

Finally, the conditional recommendations regarding ultrahypofractionation underscore the importance of shared decision making between clinicians and patients in this setting. The decision to use ultrahypofractionated EBRT at this time should follow a detailed discussion of the existing uncertainties in the risk-benefit balance associated with this treatment approach and should be informed at all stages by the patient's values and preferences.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Conflict of Interest Disclosure Statement

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Appendices

Appendix 1: Thoughts from the Patient Representative – Patrick Greany

Many patients are increasingly aware of the multitude of options and technologies available for the diagnosis and treatment of prostate cancer, thanks to the ease of finding information on the internet. However, the amount of information that is available is overwhelming and there is a need for objective, expert guidance to determine which paradigm best suits each patient, depending upon their individual circumstances. In many cases, insurance coverage dictates what the patient is able to consider, irrespective of the patient's preference.

Too often, when men consult a practitioner offering surgery, they are encouraged to have surgical intervention without being counseled about the potential for significant quality of life issues that may ensue such as impotence and urinary and bowel incontinence. The patient is often told that a prostatectomy is the "Gold Standard" and they don't hear about other options. Sometimes, the patients just want to "get it out" and don't realize that there's a significant potential that there could be a recurrence within several years.

Conversely, patients who confer with a radiation oncologist may not be made aware of the possibility of rectal toxicity. Practitioners who offer only photon IMRT may not make the patient aware of proton therapy or brachytherapy, or the possibility of combining these modalities.

Fortunately, there are a number of patient-centric support groups and organizations that serve as patient advocates, offering their services at no cost. They try to objectively assist men to become aware of state-of-the-art options and their respective evidence-based success rates and pitfalls.

Among these organizations are:

- ACS (American Cancer Society) – www.cancer.org
- PCRI (Prostate Cancer Research Institute) – www.pcri.org
- US Too (International Prostate Cancer Education & Support Network) – www.ustoo.org
- MALE CARE (Men Fighting Cancer, Together) – www.malecare.org
- PCI (Prostate Cancer International) – www.ProstateCancerInfoLink.ning.com
- PAACT (Prostate Advocates for Advanced Cancer Treatment) – http://paact.help/
- PHEN (Prostate Health Education Network – focused on African American men) – www.prostatehealthed.org/
- PROTON BOB (proton therapy advocacy) – www.protonbob.org

In addition to these groups, the Prostate Cancer Foundation (PCF, www.pcf.org) is involved in promoting funding for research on prostate cancer, as is ZERO – The End of Prostate Cancer (www.zerocancer.org). These organizations provide a great deal of information to patients and their spouses and help them become aware of the best technologies available for diagnosis, staging and treatment of prostate cancer, or the possibility of considering active surveillance.

Numerous books also are available that offer relatively comprehensive, objective guidance for men who are newly diagnosed, such as "Prostate Cancer Breakthroughs 2014", by Dr. Jay Cohen, which discusses most current options with clarity.

For patients who choose radiation, the use of hypofractionated radiation therapy is very appealing as it may offer efficacy that is similar to conventional treatment protocols, but with reduced personal expense (e.g., for housing away from home if the treating facility is at a distance) and inconvenience (especially if still employed). It could reduce the cost of treatment significantly, thereby benefitting everyone concerned, and allow more patients to be treated at a given facility. However, great care must be exercised to avoid dose escalation at the expense of safety.

From the patient's perspective, a hypofractionation protocol that achieves a high degree of efficacy in killing the cancer cells without causing untoward side effects should be sought. If this can be achieved with an ultrahypofractionation protocol, that could be ideal. However, because the principal adverse side effect of external beam radiation therapy for prostate cancer is rectal toxicity, often resulting in significant bleeding and sometimes even leading to anemia or extreme urgency, everything possible should be

done to preclude this outcome. Given the significant risk of rectal toxicity from just a few high-dose fractions, ultra-hypofractionation should be approached with great caution. The use of new technologies that assist in reducing rectal toxicity should be encouraged and further evaluated in future research studies.

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Appendix 3: Abbreviation List

- 3-D CRT: three-dimensional conformal radiation therapy
- ADT: androgen deprivation therapy
- ASCO: American Society of Clinical Oncology
- ASTRO: American Society for Radiation Oncology
- AUA: American Urological Association
- bDFS: biochemical disease-free survival
- CBCT: cone beam computed tomography
- CHHiP: Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer
- CI: confidence interval
- CTCAE: Common Terminology Criteria for Adverse Events
- CTV: clinical target volume
- DVH: dose-volume histogram
- EBRT: external beam radiation therapy
- ECCO: European Cancer Organisation
- EPIC: Expanded Prostate Index Composite
- ESTRO: European Society for Radiotherapy & Oncology

- GI: gastrointestinal
- GRADE: Grading of Recommendations Assessment, Development, and Evaluation
- GTV: gross tumor volume
- GU: genitourinary
- HRQOL: health-related quality of life
- HYPRO: Hypofractionated versus Conventionally Fractionated Radiotherapy for Patients with Prostate Cancer
- IGRT: image guided radiation therapy
- IMRT: intensity modulated radiation therapy
- IPSS: International Prostate Symptom Score
- KQ: key question
- LDR: low-dose-rate
- MCIC: minimally clinically important change
- NCCN: National Comprehensive Cancer Network
- PICO: population, intervention(s), comparator(s), outcome(s)
- PRO: patient-reported outcome
- PROFIT: Prostate Fractionated Irradiation Trial
- PSA: prostate-specific antigen
- PTV: planning target volume
- QOL: quality of life
- RCT: randomized controlled trial
- RP: radical prostatectomy
- RT: radiation therapy
- RTOG: Radiation Therapy Oncology Group
- SABR: stereotactic ablative body radiation therapy
- SBRT: stereotactic body radiation therapy
- TURP: transurethral resection of the prostate
- US: ultrasound