Hypofractionated Radiation Therapy for Localized Prostate Cancer

Background

One in eight men in the United States will develop prostate cancer in his lifetime[1]; prostate cancer is the leading type of cancer among men (age-adjusted incidence rate of 113.4/100,000 men between 2016 and 2020) and the second leading cause of cancer-related death (age-adjusted mortality rate of 18.8/100,000 men between 2016 and 2020)[2]. Seventy percent of prostate cancer diagnoses are localized disease for which external beam radiation therapy (EBRT) is a definitive and frequently used therapy[3,4].

Optimal EBRT treatment regimens with more aggressive fractionation size and dose, which may be less burdensome for patients and less resource intensive for healthcare systems[5,6], are being investigated. These treatment regimens include conventional fractionation, defined as 1.8–2.0 Gy per fraction, moderate hypofractionation, 2.4–3.4 Gy per fraction, and ultra-hypofractionation, ≥5.0 Gy per fraction. Moderate and ultra-hypofractionation schedules include fewer but higher dose fractions and shorter overall treatment durations than conventional fractionation. Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), is a form of ultra-hypofractionation that uses highly precise delivery techniques, advanced imaging, steep radiation dose gradients outside the prostate.

In their 2018 clinical practice guideline, ASTRO/ASCO/AUA issued “strong” recommendations for offering moderately hypofractionated radiation therapy to patients, noting some concerns about acute gastrointestinal toxicity and lack of long-term toxicity data. “Conditional” recommendations were offered for ultra-hypofractionated radiation therapy[5]. A recent Department of Veterans Affairs (VA) systematic review and guidance concluded that hypofractionation results in little to no difference in overall survival (high strength of evidence (SoE)), prostate cancer-specific survival (moderate SoE), biochemical recurrence-free survival (low SoE), acute or late gastrointestinal toxicity (moderate SoE), or acute or late genitourinary toxicity (moderate SoE) compared to conventional fractionation; however, the review did not present findings for moderate hypofractionation separately from ultra-hypofractionation[6].

Important new evidence on hypofractionated radiation therapy for prostate cancer has accumulated since the VA report and more is anticipated in 2024[7-14]: the ten-year follow up results for CHHiP, a large trial assessing moderate hypofractionation compared to conventional fractionation[7], and initial effectiveness results for PACE-B, the largest trial to evaluate SBRT compared to conventional fractionation/moderately hypofractionated radiotherapy[8]. Findings from the largest trial to compare ultra-hypofractionation with conventional fractionation (HYPO-RT-PC) have also been reported since publication of the previous guideline.[15] Consequently, a new systematic review will be timely for ASTRO to update its clinical practice statement, which intends to provide guidance for moderate hypofractionation separate from ultra-hypofractionation[5]. Additionally, new data on dose fractionation regimens, target volumes, treatment delivery, patient reported outcomes and quality of life may augment the guidance.

Draft Key Questions (KQs)

KQ1. For patients with localized prostate cancer receiving EBRT with curative intent, what are the benefits and harms of moderate hypofractionation compared to conventional fractionation?

> **KQ1A.** Do findings vary with respect to patient characteristics (e.g. age, race and ethnicity), pretreatment characteristics (e.g., risk group, prostate gland volume, lower urinary tract symptoms), and use of adjunctive therapies (e.g., androgen deprivation therapy)?

KQ2. For patients with localized prostate cancer receiving EBRT with curative intent, what are the benefits and harms of ultra-hypofractionation compared to moderate hypofractionation or conventional fractionation?

> **KQ2A.** Do findings vary with respect to patient characteristics (e.g. age, race and ethnicity), pretreatment characteristics (e.g., risk group, prostate gland volume, lower urinary tract symptoms), and use of adjunctive therapies (e.g., androgen deprivation therapy)?

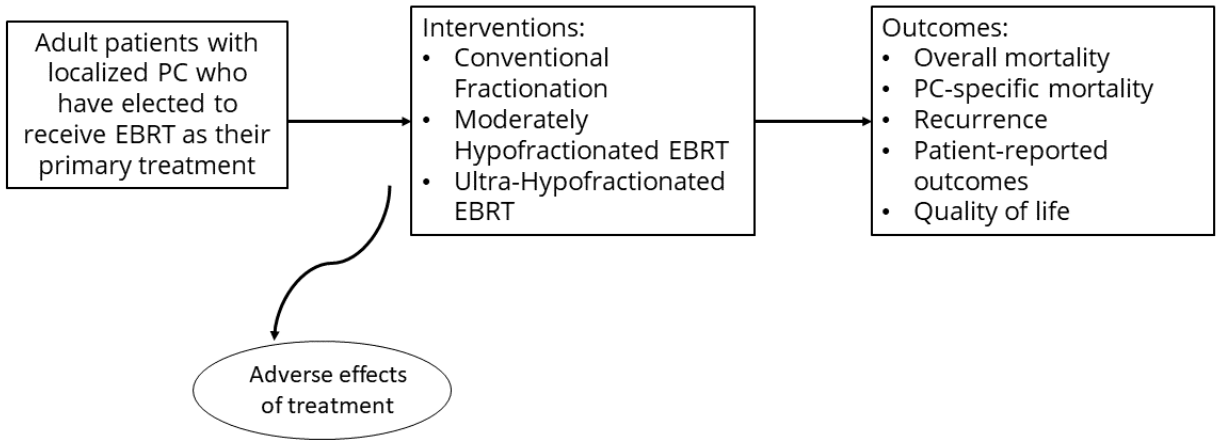
KQ3. For patients with localized prostate cancer receiving hypofractionated EBRT with curative intent, what are the benefits and harms of different dose-fractionation regimens and target volumes (e.g., prostate, seminal vesicles, pelvic lymph nodes, focal intraprostatic boosts)?

KQ4. For patients with localized prostate cancer receiving hypofractionated EBRT with curative intent, what are the benefits and harms of different treatment planning and delivery techniques?

Contextual Question: Does utilization of EBRT type (conventional fractionation, moderate hypofractionation, and ultra-hypofractionation) differ by factors such as age, race, ethnicity, socioeconomic status, or geography?

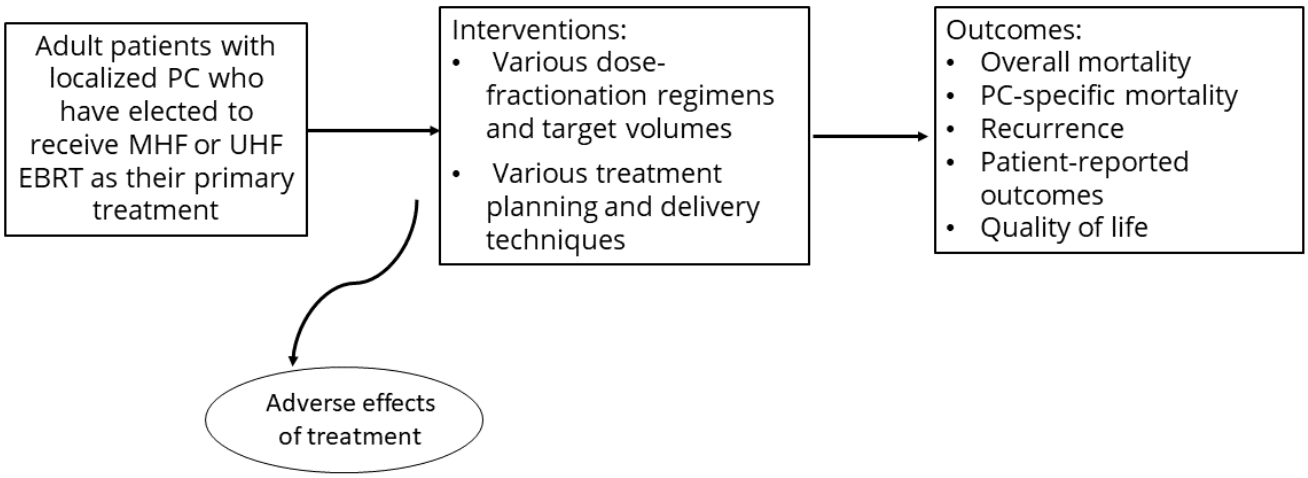
Draft Analytic Framework

Figure 1. Preliminary Analytic Framework for Key Questions 1 & 2



Note: PC = prostate cancer; EBRT = external beam radiation therapy

Figure 2. Preliminary Analytic Framework for Key Questions 3 & 4



Note: PC = prostate cancer; MHF = Moderately Hypofractionated; UHF = Ultra-Hypofractionated; EBRT = external beam radiation therapy

Scope

Table 1. PICOTSS (population, interventions, comparators, outcomes, timing, settings, study design) for KQ1-4

	KQ1	KQ2	KQ3	KQ4
Population	*For KQ1-2:* Adult patients with localized prostate cancer who have elected to receive EBRT as their primary treatment regardless of pretreatment characteristics *KQ1a and KQ2a:* Consider patient characteristics (e.g. age, race and ethnicity), pretreatment characteristics (e.g., risk group, prostate gland volume, lower urinary tract symptoms), use of adjunctive therapies (e.g., androgen deprivation therapy)		*For KQ3-4:* Adult patients with localized prostate cancer who have elected to receive MHF or UHF as their primary treatment regardless of pretreatment characteristics	

Intervention	MHF	UHF	Various dose-fractionation regimens and target volumes (e.g., prostate, seminal, vesicles, pelvic lymph nodes, focal intraprostatic boosts)	Various treatment planning and delivery techniques • Advanced imaging for target delineation • Dose-volume criteria for OARs • Image-guidance techniques • Delivery techniques • Rectal-sparing technologies • Online adaptive radiotherapy
Comparator	CF	• MHF • CF	Dose-fractionation regimens compared to each other; target volumes compared to each other [all grouped by type of hypofractionation (MHF/UHF)]	Treatment planning and delivery techniques compared to each other
Outcomes	*For KQ 1-4:* overall and prostate cancer-specific survival, local recurrence, metastases, biochemical recurrence-free survival, acute and late gastrointestinal toxicity, acute and late genitourinary toxicity, patient reported outcomes and quality of life			
Timing	*For all KQ:* any timing			
Study Design	RCT	RCT	RCT, prospective designs if RCT evidence is sparse	RCT, prospective designs if RCT evidence is sparse
Settings	*For all KQ:* all settings			

CF = Conventionally fractionated EBRT; MHF = moderately hypofractionated EBRT; UHF = ultra-hypofractionated EBRT; 3D-CRT=three-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; VMAT = volumetric modulated arc therapy; SBRT = stereotactic body radiation therapy; OARs = organs at risk

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