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High-dose-rate (HDR) brachytherapy boost in combination with external beam radiotherapy for localized prostate cancer: An evidence-based consensus statement

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ABSTRACT

PURPOSE: This guideline presents evidence-based consensus recommendations for high-dose-rate (HDR) brachytherapy boost in combination with external beam radiotherapy (EBRT) for the primary treatment of localized prostate cancer.

METHODS AND MATERIALS: The American Brachytherapy Society convened a task force for addressing key questions concerning prostate HDR brachytherapy boost with EBRT for the primary treatment of localized prostate cancer. A comprehensive literature search was conducted to identify prospective and large retrospective studies involving HDR brachytherapy combined with EBRT. Outcomes of interest included biochemical and/or disease control, toxicity, patient-reported quality of life, and the role of androgen deprivation therapy.

RESULTS: HDR brachytherapy using Ir-192 in combination with EBRT is an appropriate treatment option for men with intermediate- and high-risk prostate cancer. CT, ultrasound, and/or MRI are imaging platforms that may be utilized for treatment planning and delivery. A single implant/fraction of 15 Gy or 2 implants/fractions of 9.5-11 Gy each are acceptable regimens in combination with EBRT at a dose equivalent of 45-50.4 Gy in 1.8-2.0 Gy fractions. The addition of HDR brachytherapy is expected to improve biochemical control compared with dose escalated EBRT alone. HDR brachytherapy boost is expected to achieve similar biochemical control outcomes as a low dose rate (LDR) brachytherapy boost. Androgen deprivation therapy is recommended for men with unfavorable intermediate and high-risk disease, with varying duration dependent on cancer risk. Use of an HDR brachytherapy technique, as opposed to LDR permanent

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seeds, has been shown to have less acute genitourinary (GU) and gastrointestinal (GI) toxicity following treatment.
CONCLUSIONS: For men with intermediate- and high-risk prostate cancer, HDR brachytherapy boost is a safe and effective technique for dose-escalation that can achieve superior biochemical control compared with EBRT alone, possibly with an improved GU and GI side effect profile compared with an LDR brachytherapy technique.

Keywords: Prostate cancer; HDR brachytherapy; Brachytherapy boost; Combination

Introduction

Brachytherapy is a method to deliver high-dose radiotherapy directly to the prostate and/or seminal vesicles, while sparing surrounding organs-at-risk. The American Society of Clinical Oncology (ASCO)/Cancer Care Ontario (CCO) Joint Guideline Update in 2017 stated that for eligible patients with intermediate- and high-risk prostate cancer receiving definitive radiation, a brachytherapy boost should be *routinely offered* (1). This recommendation is largely based on the seminal ASCENDE-RT trial, which randomized men with intermediate- and high-risk prostate cancer to dose escalated external beam radiotherapy (EBRT) (whole pelvis EBRT: 46 Gy in 23 fractions followed by conformal EBRT to prostate: 32 Gy in 16 fractions; $n = 200$) versus EBRT + brachytherapy boost (whole pelvis EBRT: 46 Gy in 23 fractions followed by an I-125 implant to a minimum dose of 115 Gy to the prostate; $n = 198$). The 10-year cumulative incidence of biochemical progression was 30% in the DE-EBRT arm and 15% in the EBRT + brachytherapy arm. Multivariable analysis confirmed brachytherapy boost as an independent predictor of biochemical disease-free survival, with an adjusted hazard ratio of 2.05 for DE-EBRT versus EBRT + brachytherapy for risk of biochemical failure.

In the ASCENDE-RT trial, the brachytherapy was delivered using a permanent seed low-dose-rate (LDR) implant. The study has been criticized for having an unacceptably high rate of grade 3+ genitourinary (GU) toxicities (5-year cumulative incidence 18.4% vs. 5.2%, 5-year prevalence 8.6% vs. 2.2%), predominantly urethral strictures, which is thought to be, in part, related to the implantation technique with excessive dose delivered caudally at the genitourinary diaphragm (2). Subsequent studies, also using combined prostate LDR brachytherapy and EBRT, have shown much lower rates of grade 3+ GU toxicities (~2%), stressing the importance of technique on optimal long-term quality of life outcomes (3,4). These and other studies support LDR brachytherapy boost as a proven method of dose escalation with decades of follow-up and endorsement by numerous expert consensus groups (1,5–7).

Another method of brachytherapy is high-dose-rate (HDR) brachytherapy, which has advantageous properties including temporary implantation of the radioactive source (Ir-192), more consistent dose coverage of the prostate ± proximal seminal vesicles, improved dose modulation around the rectum, bladder, and urethra through inverse treatment planning, and a more rapid toxicity resolution (4,8–10). Both LDR and HDR brachytherapy boost are supported by professional guidelines, and the choice between the 2 is often determined by physician, patient, and/or treatment facility resources (1,5,7).

The American Brachytherapy Society (ABS) has previously published guidelines for LDR brachytherapy boost in combination with EBRT in 2021 (6). This current consensus provides recommendations and accompanying support for the use of HDR brachytherapy in combination with EBRT for patients with unfavorable intermediate- and high-risk prostate cancer.

Methods

In May 2024, the American Brachytherapy Society Board of Directors approved a process to establish consensus guidelines regarding the use of HDR brachytherapy in combination with external beam radiotherapy for men with localized prostate cancer. The guidelines were developed utilizing a modified Delphi approach, based on the best available data identified in a formal systematic review (11). The guideline panel involved in this process was a collaboration of brachytherapists across the United States and Canada created to review and report the clinical and technologic evolution of combination EBRT with HDR brachytherapy. We searched MEDLINE and PubMed between March and October 2024 using a combination of the following terms: “prostate”, “brachytherapy”, “boost”, “high-dose-rate”, “implant”, “combination”. Of the 247 articles that were identified and reviewed, 21 were selected for review based on adequate sample size ($n > 50$ in each comparator arm for nonrandomized studies), follow-up time (≥5 years for efficacy endpoints, ≥6 months for toxicity endpoints), and relevance to the key questions defined below. In total, 22 original studies were selected for this review. The initial screening of abstracts/manuscripts was performed by 1 author (S Patel) followed by review and validation by another author (M Kamrava).

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Table 1
Guideline recommendations for key questions (KQ) based on systematic review.

Guideline recommendation	Strength of recommendation	Quality of evidence
KQ1: How does efficacy compare between EBRT alone versus combination EBRT plus HDR brachytherapy boost?		
-Biochemical control is improved with the addition of an HDR brachytherapy boost for patients with intermediate- and high-risk disease.	Strong	High
KQ2: How does efficacy compare with HDR brachytherapy boost compared with LDR brachytherapy boost?		
-Biochemical control is expected to be similar between HDR versus LDR boosts.	Strong	High
KQ3: How does toxicity compare with HDR brachytherapy boost compared with LDR brachytherapy boost?		
-Acute urinary toxicity may be lower with HDR compared with LDR; long-term urinary toxicity is expected to be similar	Strong	Moderate
-Acute and long-term bowel toxicity may be lower with HDR compared with LDR.	Strong	Moderate
KQ4: What dose and fractionation schemes are preferred when utilizing an HDR brachytherapy boost?		
-15 Gy x1	Strong	Moderate
-9.5-11 Gy x 2	Strong	Moderate
KQ5: What is the role of ADT when using combination EBRT with HDR brachytherapy boost?		
-Improving disease control outcomes for unfavorable intermediate- and high-risk prostate cancer.	Strong	High
KQ6: What is the optimal duration of ADT when using combination EBRT with HDR brachytherapy boost for unfavorable intermediate- and high-risk prostate cancer?*		
-4-*6 months (intermediate-risk)*	Strong	High
*-6 months (high-risk)**	Weak	Moderate
-12+ months (high-risk)	Strong	High
KQ7: What are strategies for improving toxicity and quality of life following an HDR implant?^		
-Urethra, Rectal, Bladder Dosimetry Constraints	Strong	Moderate
-Alpha-blockers	Strong	Moderate
KQ8: How are HDR brachytherapy boost plans evaluated?^		
-CT	Strong	Low
-Ultrasound	Strong	Low
-MRI	Strong	Low
KQ9: What is the optimal sequencing of HDR brachytherapy with EBRT?		
-HDR brachytherapy can be administered before or after EBRT	Strong	Moderate
KQ10: What is an appropriate EBRT dose/fractionation regimen to use in combination with HDR brachytherapy boost?		
-45-50.4 Gy in 1.8-2.0 Gy fractions (prostate/SV +/- pelvic nodes)	Strong	High
-37 Gy in 2.5 Gy fractions (prostate/SV only)	Strong	Moderate
-25 Gy in 5 fractions (prostate/SV +/- pelvic nodes)	Weak#	Moderate
KQ11: Which patients are suitable candidates for HDR brachytherapy boost?^		
-Sufficient life expectancy	Strong	Expert Opinion
-Suitable prostate anatomy/volume	Strong	Expert Opinion
-Baseline urinary function	Strong	Expert Opinion

^ KQs not included in the systematic review.
* ADT duration may be individualized based on risk-tier, patient comorbidity, patient quality-of-life priorities.
# Agreement amongst panel was 69.23%, not meeting consensus threshold of ≥70%.

Key questions that comprehensively addressed disease control, toxicity and patient-reported outcomes, fractionation regimens, and ADT use were formulated. A draft of the consensus recommendations was initially reviewed by a smaller panel (S Patel, M Kamrava, J Crook, M Kollmeier, G Morton, D Krauss). Modified recommendations were then disseminated to the full consensus panel, and members rated their level of agreement with each recommendation. Table 1 shows each guideline recommendation for key questions utilized in this statement. Key questions 1 through 7 were derived from systematic review, while the remaining questions (addressing techniques for treatment planning/evaluation and patient suitability for HDR brachytherapy boost) were answered via expert opinion alone due to the dearth of robust studies around these topics. For each key question, the strength of recommendation (weak, strong) and strength of evidence (low, moderate, high) were graded based on previously published

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ABS consensus guidelines (6). Final strength of recommendations in Table 1 were based on ≥70% agreement of the expert panel. Agreement rates for each key question are shown in Supplemental Table.

KQ1: How does treatment efficacy compare between EBRT alone versus combination EBRT plus HDR brachytherapy boost?

Given the accepted understanding of the radiobiology of prostate cancer with a low alpha-beta relative to surrounding normal tissue, a higher sensitivity to dose-fractionation is expected. The degree of dose escalation achievable with HDR brachytherapy, compared to dose-escalated EBRT alone, is therefore potentially radiobiologically more lethal for prostate cancer cells which could translate into improved long-term oncologic outcomes (12,13).

There have been 4 head-to-head studies comparing EBRT alone versus EBRT with HDR brachytherapy boost for patients with localized prostate cancer, as detailed in Table 2. The first, and most robust, report of improved disease outcomes with the addition of HDR brachytherapy with EBRT came from a prospective, randomized controlled trial by Hoskin and colleagues in patients with T1-3N0M0, PSA <50 disease (14). After over 10 years of follow-up, the addition of an HDR brachytherapy boost improved 12-year recurrence free survival from 27% to 48% ($p=0.008$), with a hazard ratio of 0.29 (95% CI, 0.11–0.47). The TROG 03.04 RADAR trial (15) was a 2×2 randomization between short- and intermediate-term ADT with or without zoledronic acid, and a posthoc analysis was carried out comparing EBRT alone versus in combination with an HDR brachytherapy boost in patients with clinical T2b or higher, Gleason ≥7, and/or PSA ≥10 disease. Patients received either 6 or 18 months of ADT. After over 10 years of follow-up, rates of distant metastasis were significantly improved with the addition of HDR brachytherapy (14.9% with HDR boost versus 20.4-22.4% with EBRT alone depending on dose). Compared with men treated with modern dose-escalated EBRT alone of 74 Gy, HDR brachytherapy boost trended to provide a distant metastasis benefit with a hazard ratio of 0.75 (95% CI 0.56–1.01, $p=0.06$). Finally, 2 large retrospective analyses (16,17) were recently completed, comparing patients with predominantly intermediate and high-risk prostate cancer treated with EBRT alone (median dose: 70 Gy in 35 fractions) or EBRT (46 Gy) with HDR brachytherapy boost (18 Gy in 3 fractions or 20 Gy in 4 fractions). In the Kent et al. analysis, 5-, 10- and 15-year prostate cancer specific survival (PCSS) was improved with HDR brachytherapy boost and particularly notable in high-risk men (15-year PCSS 85% vs. 69%; $p=0.01$). In the Tamihardja et al. (17) study, a propensity-score matched analysis comparing EBRT (mean dose 76.23 Gy) versus EBRT (46 Gy) with HDR brachytherapy (18 Gy in 2 fractions) showed that 10-year metastasis-free survival was numerically higher with HDR brachytherapy (87.0% vs. 82.9%), but statistical significance was not reached.

KQ2: How does efficacy compare between HDR brachytherapy boost versus LDR brachytherapy boost?

Key studies comparing HDR versus LDR boost are shown in Table 3. Perhaps the most robust study, performed by Crook et al., (18) was a randomized controlled trial comparing HDR versus LDR brachytherapy boost in combination with EBRT in patients with unfavorable intermediate or high-risk prostate cancer. 8-year biochemical progression free survival (bPFS) was nearly identical (86% for HDR, 85% for LDR); when using a surgical definition of biochemical control of PSA ≤0.2, 4-year PSA control was 81% for HDR boost versus 83% for LDR boost ($p=0.91$). Two retrospective, single institution series (19,20) also compared HDR versus LDR brachytherapy boost. Imai et al. (19) included patients with clinical T1-3aN0 and PSA <100 disease; with a median follow-up of over 6 years in each group, 5-year bPFS was similar between the 2 techniques (86.2% for HDR and 85.6% for LDR, $p=0.89$). Yamazaki et al. (20) included patients with similar disease characteristics and follow-up time; 5-year bPFS for unfavorable intermediate-risk patients was 97.2% versus 96.2% for HDR boost and LDR boost, respectively ($p=0.66$); 5-year bPFS for high-risk patients was 95.7% versus 95.5% for HDR boost and LDR boost, respectively ($p=0.86$). Finally, a large database analysis using the National Cancer Database (21) found no difference in overall survival outcomes between patients with unfavorable intermediate or high-risk prostate cancer treated with an HDR versus LDR brachytherapy boost (5-year survival hazard ratio 1.03, 95% CI, 0.96-1.11). Based on the currently available data, PSA control rates within 5 to 10 years appear to be similar between LDR and HDR boost. Continued follow-up of patients is needed to ensure that this trend continues to hold for patients beyond 10 years after treatment. Details regarding study cohort, ADT use (when available), and outcome measures for each of these studies is detailed in Table 3.

KQ3: How do toxicity outcomes compare between HDR brachytherapy boost versus LDR brachytherapy boost?

The addition of a brachytherapy boost with EBRT has been shown to improve long-term biochemical control in the ASCENDE-RT prospective randomized trial, but concerns have been raised about the potential for increased toxicity suggested from this trial. At 5 years, the cumulative incidence of grade 3 GU toxicity was higher in the brachytherapy boost arm (18.4% vs. 5.2%; $p<0.001$); however, most resolved following intervention. The additional toxicity, namely GU, is thought to be technique-related (e.g. excessive dose deposited at the external urinary sphincter), as subsequent LDR boost studies with more stringent preimplant planning have shown lower rates of long-term GU toxicities. For example, in the TRIP trial (3) which investigated ADT duration in a cohort of high-risk prostate cancer patients receiving combination EBRT with LDR brachytherapy, the incidence of grade 3 GU tox-

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Table 2
Comparative outcome studies comparing EBRT alone versus EBRT plus HDR brachytherapy boost in intermediate- or high-risk patients.

Study	Disease characteristic	Treatment	BED (Gy) (α/β 1.5)	N	Age, median	Follow-up time, median	ADT use	Primary outcome
Hoskin et al. (14)[b]	T1-3N0M0 PSA<50 No prior TURP	EBRT+HDR[a] EBRT[b] *Randomized*[c]	217.68 160.53	110 106	70 (range 47–80)	131 months	76%; Neoadjuvant/concurrent; duration not reported	6-/12-yr RFS: 71%/48% 6-/12-yr RFS: 55%/27% $P=0.008$ HR (EBRT+HDR vs. EBRT): 0.29 (95% CI 0.11–0.47), $P=0.001$
TROG 03.04 RADAR Denham et al. (15)	T2b-4N0M0 Gleason ≥7 PSA ≥10	EBRT+HDR[d] EBRT[e]	211.33 154-172.67	237 814	68.7 (range 48-85)	10.5 years	100%; 6 or 18 months	DM: 14.9% DM: 22.4% (66 Gy), 22.0% (70 Gy), 20.4% (74 Gy) HR (HDR vs. 70 Gy) 0.68 (95% CI 0.57–0.80), P <0.0001 HR (HDR vs. 74 Gy) 0.75 (95% CI 0.56–1.01), $P=0.06$
Kent et al. (16)	NCCN intermediate and high risk	EBRT+HDR[f] EBRT[g]	197.33 163.33	215 439	72.3 68.9	12.2 years		10-yr PCSM: 93% 15-yr PCSM: 87% 10-yr PCSM: 88% 15-yr PCSM: 79% P <0.037
Tamihardja et al. (17)sss	NCCN low, intermediate, high risk	EBRT+HDR[h] EBRT[i]	233.33 192.28	258 258 1:1-matched	71.0 72.3	95.3 months	51.9% 53.5% Median duration 20 months	10-yr MFS: 87.0% 10-yr MFS: 82.9% $P=0.195$

[a] EBRT+HDR: 35.75 Gy in 13 fractions; HDR 17 Gy in 2 fractions over 24 hours.
[b] EBRT: 55 Gy in 20 fractions.
[c] Randomized controlled trial.
[d] EBRT+HDR: 46 Gy in 23 fractions; HDR 19.5 Gy in 3 fractions.
[e] EBRT: 66, 70, or 74 Gy.
[f] EBRT+HDR: 46 Gy in 23 fractions; HDR median 18 Gy in 3 fractions.
[g] EBRT: 70 Gy.
[h] EBRT+HDR: 46 Gy in 23 fractions + HDR 18 Gy in 2 fractions.
[i] EBRT: 76 Gy in 33 fractions.

Table 3
Comparative outcome studies comparing HDR brachytherapy boost versus LDR brachytherapy boost in combination with EBRT.

Study	Disease characteristic	Treatment	N	Age, median	Follow-up time, median	ADT use	Primary outcome
Crook et al. (18)	NCCN unfavorable intermediate, high risk	EBRT + HDR	108	71	74 months	76% overall	4-year PSA ≤0.2: 81% 5-year bPFS: 94% 8-year bPFS: 86%
		EBRT + LDR *randomized*[a]	87				4-year PSA ≤0.2: 83% 5-year bPFS: 90% 8-year bPFS: 85% $P = 0.91$ (4-year PSA ≤0.2)
Imai et al. (19)	cT1-3aN0M0, PSA <100	EBRT + HDR	252	68.7	98.9 months	94% (mean 29.7 months)	5-yr bPFS: 86.2%
		EBRT + LDR	66	70.5	77.5 months	43.9% (mean 9.28 months)	5-yr bPFS: 85.6% $P = 0.89$
Yamazaki et al. (20)	cT1-3aN0M0, PSA <50	EBRT + HDR[b]	924	71	70 months	94%	5-yr bPFS: 97.2% (unfav int risk), 95.7% (high risk)
		EBRT + LDR	69	69	84 months	80%	5-yr bPFS: 96.2 (unfav int risk), 95.5% (high risk) $P = 0.664$ (unfav int risk), 0.859 (high risk)
King et al. (21)[a]	NCCN unfavorable intermediate, high risk	EBRT + HDR	8526	67.1	5 years	40.4%	OS: adjusted HR (LDR vs. HDR) 1.03 (95% CI 0.96–1.11)
		EBRT+LDR	9877	66.7		43.1%	$P = 0.38$

[a] HDR boost included 11 Gy in 1 fraction, 18-21 Gy in 2 fractions, 21 Gy in 3 fractions, 25-31.5 Gy in 5 fractions.

icity <1% within 3 years. Patient selection, technique, and implant dosimetry evaluation are important to mitigate toxicity risks following either LDR or HDR brachytherapy boost.

Nonetheless, there is concern that the improved biochemical control with brachytherapy-based dose escalation may not be worth the additional toxicity risk, given alternative methods such as partial gland dose escalation (i.e., microboosting), which can improve PSA control while remaining isotoxic (22). Due to the slow dose rate of LDR sources, a prolonged inflammatory effect may contribute to the acute and subacute toxicity profile of LDR, which may be improved with an HDR approach. Indeed, a posthoc analysis of the Australian TROG 03.04 RADAR trial, which included patients treated with dose-escalated EBRT to 74 Gy or combination EBRT to 46 Gy with an HDR brachytherapy boost of 19.5 Gy in 3 fractions, showed slower recovery of urinary quality-of-life after HDR brachytherapy boost within 1.5 years, yet no long-term differences in urinary quality-of-life beyond 29 months (23).

Notable studies comparing toxicity and patient-reported outcomes between HDR versus LDR brachytherapy boost is shown in Table 4. Most recently, Crook et al. (4) performed a prospective randomized trial comparing HDR versus LDR brachytherapy boost in combination with EBRT in men with unfavorable intermediate or high-risk prostate cancer. Patient-reported outcomes were compared using the Expanded Prostate Index Composite (EPIC-26) and International Prostate Symptom Score (IPSS) questionnaires; at 6 months post-treatment completion, both EPIC-26 urinary domain scores and IPSS composite scores were significantly improved with HDR compared with LDR brachytherapy boost. Specifically, EPIC urinary scores decreased at 1 month for HDR boost patients but recovered by 6 months; for LDR boost patients, EPIC urinary scores reached a nadir at 3 months with recovery extending out to 18 months post-treatment. Beyond 18 months, urinary quality-of-life was similar between the 2 arms. In terms of bowel toxicity, EPIC bowel domain scores were significantly improved with HDR compared with LDR boost. Specifically, bowel quality-of-life reached a nadir at 12 months for both arms; however, patients receiving HDR boost recovered near baseline and maintained higher quality-of-life scores extending out to 5 years post-treatment, compared with patients receiving LDR boost. The LDR boost bowel quality-of-life decline was greater than the predefined minimum clinically important difference out to 5 years, while this threshold was not achieved for men receiving HDR boost. These results are con-

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Table 4
Comparative toxicity and quality of life studies between HDR versus LDR brachytherapy boost.

Study	Treatment	N	Rectal spacer	GU toxicity	GI toxicity	Multivariable analysis
Crook et al. (4)[a]	HDR boost	108	None	EPIC 84 ± 13 IPSS 8.0 1 G3, 7 G2 (6.7%)	EPIC 89 ± 12 No G3, 5 G2 (4.8%)	
	LDR boost	87		EPIC 77 ± 14 IPSS 11.8 1 G3, 2 G2 (2.4%)	EPIC 83 ± 16 1 G3, 9 G2 (10.8%)	
	Randomized[b]			$P = 0.001$ (EPIC) $P = 0.0002$ (IPSS)	$P = 0.02$ (EPIC)	
Kollmeier et al. (24)[b]	HDR boost	59	73%	G2 5.1%	G2 3%	Ref
	LDR boost	40	18%	G2 45%	G2 5%	HR G2+ GU toxicity: 8.14 (95% CI 2.82-23.5)
Dhere et al. (25)[a]	HDR boost	55	None	G2+ 42.9%	G2+ 2.0%	
	LDR boost	51		G2+ 67.5%	G2+ 2.6%	
				$P < .001$	$P = 0.99$	
Parry et al. (26)[c]	HDR boost	2,765	None	G2+ 16.6% (95% 15.1–18.2) EPIC 78.9 (95% 77.4–80.3)	G2+ 16.7% (95% 15.2–18.2) EPIC 85.8 (95% 84.4–87.2)	sHR (LDR boost ref)
	LDR boost	330		G2+ 15.8% (95% 11.9–20.2) EPIC 72.2 (95% 66.9–77.5)	G2+ 32.2% (95% 26.9–37.7) EPIC 77.3 (95% 72.2–82.5)	GU: no SS difference GI 0.48 (95% CI 0.34–0.70)
				EPIC $P < 0.001$	EPIC $P < 0.001$	

[a] 6-month toxicity; EPIC lower scores indicate worse symptoms, IPSS higher scores indicate worse symptoms.
[b] 12-month toxicity.
[c] 5-year cumulative incidence of toxicity; EPIC (urinary irritation/obstruction, bowel) lower scores indicate worse symptoms.

sistent with that seen in several other large institutional retrospective and population-based studies, as listed in Table 4. Notably, across these studies, physician-reported and patient-reported urinary and/or bowel toxicity was improved with HDR boost compared with LDR boost, predominantly within 6 to 12 months after treatment completion.

KQ4: What dose and fractionation schemes are preferred when utilizing an HDR brachytherapy boost?

A wide range of dose and fractionation schedules of HDR brachytherapy in the boost setting have been used (27–34). Table 5 summarizes larger studies that attempted to compare oncologic outcomes and toxicity between various HDR regimens. Notably, there have been no head-to-head randomized trials comparing efficacy and toxicity between the various approaches. The phase II RTOG 0321 trial (27), which prospectively evaluated long-term toxicity and efficacy of combination EBRT 45 Gy in 25 fractions with HDR brachytherapy 9.5 Gy x 2 in a single implant for unfavorable risk prostate cancer, used a relatively low dose, compared with modern standards, of a BED ~238 Gy (assuming alpha/beta of 1.5); the 10-year local control rate was 98% and biochemical failure rate was 23%. In 2011, Martinez et al. (35) compared 2 cohorts based on biological effective dose (BED) >268 versus ≤268 Gy achieved; all patients received EBRT 46 Gy in 23 fractions. Patients who underwent an HDR brachytherapy boost of 5.5-6.5 Gy x 3 or 8.25-10 Gy x2 received a BED ≤268 Gy, while those who underwent 10.5-11.5 Gy x2 achieved a BED >268 Gy. The 10-year biochemical failure rate, defined per Phoenix criteria, was 43.1% versus 18.9% for those treated with BED ≤268 versus >268 Gy, respectively ($p < 0.001$); 10-year distant metastasis rate was 12.4% versus 5.7%, respectively ($p = 0.028$). On multivariable analysis, the hazard ratio for 10-year biochemical failure was 0.586 (95% CI 0.377-0.910; $p = 0.017$), demonstrating the importance of achieving a BED >268 when utilizing combination EBRT with HDR brachytherapy. Notably, grade 3 urinary toxicity was similarly low between dose schedules.

Subsequently, Helou et al. (36) conducted a comparative analysis between 2 sequential phase II trials: (1) HDR 15 Gy x 1 followed by EBRT 37.5 Gy in 15 fractions (cumulative BED 265 Gy) versus (2) HDR 10 Gy x 2 followed by EBRT 45 Gy in 25 fractions (cumulative BED 253 Gy). The 5-year biochemical progression free survival, using Phoenix criteria, was 92.7% when using HDR 10 Gy x 2 versus 97.4% when using HDR 15 Gy x1 ($p = 0.995$); the hazard ratio for 10-year biochemical control, defined as PSA nadir <0.4, on multivariable analysis was 1.078 (95% CI, 0.703–1.652, $p = 0.729$). As such, this study showed no

Table 5
Comparative outcomes and toxicity between various HDR fractionation schedules.

Study	BED (Gy)[a]	HDR dose regimen	N	Primary outcome	Multivariable analysis	Toxicity
RTOG 0321 (27)	238	9.5 Gy x 2 (single implant)	129	5-yr bF (Phoenix): 14% 10-yr bF (Phoenix): 23%		G3 GU: 5% G3 GI: 4%
Martinez et al. (35)	≤268	5.5-6.5 Gy x 3, 8.25-8.75 × 2	167	10-yr bF (Phoenix): 43.1% 10-yr LRF: 14.3% 10-yr DM: 12.4%		G3 dysuria: 2% G3 frequency/urgency: 1% G3 hematuria: 2%
	>268	9.5-11.5 × 2	305	10-yr bF (Phoenix): 18.9% 10-yr LRF: 2.8% 10-yr DM: 5.7% P (bF) <.001 P (LRF) = .001 P (DM) = .028	HR of 10-yr bF: 0.586 (0.377–0.910), $P = 0.017$	G3 dysuria: 1% G3 frequency/urgency: 1% G3 hematuria: 3%
Helou et al. (36)	253	10 Gy x 2	60	5 yr bPFS (Phoenix): 92.7%		
	265	15 Gy x 1	123	5-yr bPFS (Phoenix: 97.4% $P = 0.995$	HR (PSA nadir <0.4): 1.078 (0.703–1.652) $P = 0.729$	
Vigneault et al. (37)	<250	6-6.5 Gy x 3, 9.5 Gy x 2	79	5-yr bPFS (Phoenix): 97.3% 5-yr PSA <0.2: 68.6%	OR of 5-yr PSA ≥0.2: Ref	G3+ GU: 0%
	250-260	10 Gy x 2	497	5-yr bPFS (Phoenix): 94.3% 5-yr PSA <0.2: 78.7%	0.639 (0.356–1.148), $P = 0.134$	G3+ GU: 0% acute, 1.7% late
	>260	15 Gy x 1, 10.5 Gy x 2	256	5-yr bPFS (Phoenix): 94.9% 5-yr PSA <0.2: 86.7% P (Phoenix) = .453 P (PSA <0.2) = .005	0.350 (0.156–0.782), $P = 0.011$	G3+ GU: 4.7% acute, 4.9% late

External beam radiotherapy (EBRT) doses used:.
-Vigneault et al.: 40 Gy in 20 fractions, 44 Gy in 22 fractions, 45 Gy in 25 fractions, 36 Gy in 12 fractions; target volume included prostate and seminal vesicles ± pelvic nodes.
-Martinez et al.: 46 Gy in 23 fractions.
-Helou et al.: 45 Gy in 25 fractions with 10 Gy x 2 HDR; 37.5 Gy in 15 fractions with 15 Gy x 1 HDR.
[a] BED = biological equivalent dose, calculated assuming an alpha/beta ~1.5.

clear differences in outcomes between a single HDR fraction of 15 Gy versus a 2-fraction approach of 20 Gy.

Finally, Vigneault et al. (37) compared 3 BED doses utilizing a range of HDR schedules in combination with 40–45 Gy in 20–25 fractions or 36 Gy in 12 fractions of EBRT: HDR 6-6.5 Gy x 3 or 9.5 Gy x 2 (BED <250 Gy), HDR 10 Gy x 2 (BED 250–260 Gy), and HDR 10.5 Gy x 2 or 15 Gy x 1 (BED >260 Gy). The 5-year biochemical progression free survival, defined by Phoenix criteria, did not significantly differ between the 3 groups; however, when defining biochemical control as PSA <0.2, the 5-year biochemical control was significantly improved when achieving a BED >260 Gy. Acute grade 3+ genitourinary was modestly higher with BED >260 Gy (HDR 10.5 Gy x 2 or 15 Gy x 1), but rates of toxicity were overall very low.

Current cooperative trials and professional guidelines (38) advocate for either 15 Gy x 1 or a range of 9.5-11 Gy x 2 when using HDR brachytherapy in combination with EBRT for intermediate and high risk prostate cancer. Single fraction of 15 Gy may be the preferred approach given BED >260 Gy, prospective comparative data showing similar outcomes as LDR 110 Gy boost (18), and the least resource-intensive approach for the clinic and patient with a single implant, plan, and delivery.

KQ5/6: What is the role and duration of ADT with EBRT plus HDR Brachytherapy?

The role of ADT with radiation for prostate cancer has been long-established. In addition to its local cytoreductive effects and potential cytotoxic effect on micrometastatic disease, laboratory data has identified the effect of ADT on the local tumor microenvironment that promotes radiosensitization, such as reduction of tumor hypoxia and enhancement of oxidative stress following radiation (39). More recent data suggests that androgen receptor (AR) regulates a transcriptional program of DNA repair genes, and

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with that, AR promotes prostate cancer radioresistance by promoting postradiation DNA repair. As such, inhibiting AR via ADT promotes radiosensitization via inhibition of DNA repair after radiation-induced double-stranded breaks (40).

However, the role of androgen deprivation therapy (ADT) in patients treated with "extreme" dose-escalated radiation, as that achieved with combination EBRT plus brachytherapy, remains poorly studied. The ASCENDE-RT trial (41) supports the use of 12 months of ADT with combination EBRT plus brachytherapy for men with high-risk prostate cancer (which comprised approximately 70% of the trial cohort). In another study (42), a pooled multicenter cohort analysis of over 3000 patients with high-risk prostate cancer receiving definitive radiation and ADT, there was a significant interaction between treatment type (i.e., EBRT alone versus EBRT plus brachytherapy) and ADT duration; specifically, natural cubic spline analysis identified a minimum ADT duration threshold of 12 months for men treated with EBRT plus brachytherapy for optimal effect on distant metastasis free survival (compared with a minimum duration threshold of 26 months for men treated with EBRT alone).

RTOG 0815 (43) was a randomized trial comparing radiation alone versus radiation plus 6 months ADT in men with intermediate-risk prostate cancer. In the overall cohort, after a median follow-up of over 6 years, addition of short-course ADT resulted in small but statistically significant improvements in rates of distant metastasis and prostate cancer-specific mortality; no overall survival benefit has been observed. Notably, on subgroup analysis restricted to patients receiving combination EBRT plus brachytherapy (HDR or LDR), the benefit of short-course ADT on distant metastasis remained (98.4% vs 94.9%, p <0.001). Additionally, on multivariable analysis, there was a trend toward improved overall survival with 6 months of ADT in patients receiving combination EBRT plus LDR brachytherapy (adjusted HR 0.31, 95% CI, 0.10–1.0, $p=0.05$). Notably, the number of patients receiving HDR boost was too small for multivariable analysis.

However, use of ADT, even short courses of 4-6 months, can have deleterious effects on quality of life, including physical function/vitality, cognition, and sexual function. Additionally, ADT is associated with metabolic disease, cardiovascular morbidity, and other-cause mortality (44–48); as such, efforts to mitigate the use of ADT in patients with otherwise curable prostate cancer are ongoing, such as the NRG GU010 trial, which is randomizing men with unfavorable intermediate-risk prostate cancer and low Decipher genomic classifications core to 6 months ADT versus no ADT with definitive radiation therapy.

The TRIP trial (3) is a multicenter, phase 3 randomized trial across Japan comparing 6 versus 30 months of ADT with EBRT plus I-125 LDR brachytherapy in patients with high-risk prostate cancer. After a median follow-up of over 9 years, the cumulative incidence of biochemical progression (per Phoenix criteria) at 7 years in the 6- versus 30-month ADT arm was 9.0% versus 8.0%, respectively ($p=0.65$). However, this study was designed as a superiority study, with the hypothesis that 30 months of ADT would improve biochemical control compared with 6 months; given that long-term ADT is the standard of care for men with high-risk prostate cancer, a noninferiority study remains warranted to confirm whether truncated duration of ADT in this high-risk cohort is safe.

The duration of ADT with extreme dose-escalated radiation has also been scrutinized in the intermediate-risk population. The SHIP0804 trial (49) is a multicenter, phase 3 randomized trial across Japan of men with D'Amico intermediate-risk prostate cancer treated with I-125 LDR brachytherapy 144 Gy, comparing 3 months of neoadjuvant ADT ± 9 months of adjuvant ADT (i.e., cumulative 3 months ADT versus 12 months ADT). After a median follow-up of over 11 years, the 10-year bPFS was 82.9% with 12 months ADT versus 78.4% with 3 months ADT ($p=0.51$). These findings persisted even in subgroup analysis based on number of intermediate-risk factors (1, 2, or 3).

Notably, these prospective studies exclusively or predominantly utilized LDR brachytherapy. While results would not be expected to differ (18), there have been no head-to-head trials comparing the role of concomitant ADT in men with intermediate and/or high-risk prostate cancer treated with combination EBRT plus HDR brachytherapy. There have been single-institution retrospective studies, however, which have had mixed results with respect to the benefit of ADT on oncologic outcomes (50–53). These studies are limited due to imbalances in comparative groups, outdated EBRT and/or HDR brachytherapy dosing regimens, inconsistent ADT durations, and suboptimal sequencing of ADT with respect to radiation therapy. More recent analysis including more contemporary regimens are detailed in Table 6. Specifically, 1 retrospective study by Ishiyama et al. (54) in 2017 of predominantly high-risk prostate cancer patients compared EBRT plus HDR brachytherapy with versus without ADT (most commonly long course with both neoadjuvant and adjuvant component of ADT). After a median follow-up of 66 months, the adjusted hazard ratio for disease-free survival was 0.55 (95%, CI 0.40–0.76, p <0.0001) and for biochemical control was 0.48 (95% CI, 0.36–0.64, p <0.0001). Additionally, perhaps the most robust data indirectly comparing the role of ADT in patients treated with EBRT plus HDR brachytherapy was the Australian multicenter TROG 03.04 RADAR (55), which was a 2×2 factorial randomized trial of men with predominantly high-risk prostate cancer, randomized to receive 6 versus 18 months of ADT as well as randomized between 0 versus 18 months of zolendronic acid. Enrolled patients received dose-escalated EBRT or EBRT with HDR brachytherapy. On subgroup analysis confined to men receiving EBRT plus HDR brachytherapy, longer-

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Table 6
Contemporary studies comparing role and duration of ADT with EBRT + HDR brachytherapy boost in men with intermediate- and high-risk prostate cancer.

Study	Disease characteristic	Treatment	N	Age, median	Follow-up time, median	Primary outcome
Ishiyama et al. (54)	NCCN risk distribution: 31% intermediate, 49% high, 14% very-high	EBRT + HDR + ADT[a]	2403	69 (SD 6.46)	66 months	[b]HR (cDFS): 0.55 (95% CI 0.40-0.76) [b]HR (PSA control): 0.48 (95% CI 0.36-0.64)
		EBRT + HDR alone	699			Ref
						P <0.0001
TROG 03.04 RADAR, Joseph et al. (55)	T2b-4N0M0, or T2a and GS ≥7 and PSA ≥10 (66.3% of overall cohort was NCCN high risk; 79.6% was D'Amico high risk)	EBRT + HDR + 6 mo ADT	114	69 (range 48–85)	10.5 years	Distant Progression, 18mo vs. 6mo: All patients: 0.70 (95% CI 0.56–0.87) EBRT+HDR: 0.61 (95% CI 0.38–0.97)
		EBRT + HDR + 18 mo ADT	123			[b]*no interaction between ADT duration and RT dose (p = 0.76)*

[a] Median HDR dose was 18 Gy (IQR 18–24), median HDR fractional dose was 9 Gy (IQR 6.4-9.0); median EBRT dose was 39 Gy (IQR 39–45), median EBRT fractional dose was 3 Gy (IQR 2.5–3.0).aMean duration of neoadjuvant and adjuvant ADT was 8.6 ± 7.4 months and 27.9 ± 12.9 months, respectively.
[b] Results include patients who received neoadjuvant + adjuvant ADT only.

course ADT of 18 months was associated with significantly improved rates of distant metastasis compared to 6 months of ADT (adjusted hazard ratio 0.61, 95% CI 0.38–0.97). Of note, in the overall cohort analysis, there was no interaction between ADT duration and RT dose (i.e., dose-escalated EBRT versus EBRT plus HDR boost), suggesting that the benefit of long-term ADT in this high-risk cohort was independent of use of an HDR brachytherapy boost or not. A major limitation of this analysis, however, is that the HDR brachytherapy dose utilized in the TROG 03.04 RADAR trial was lower (i.e., BED <260 Gy) than optimal contemporary regimens; whether the oncologic benefit of long-term ADT remains in men treated with optimal "extreme" dose-escalated regimens of EBRT plus HDR brachytherapy remains unclear.

Nonetheless, taking the above studies into consideration, decisions regarding utilization and duration of ADT for men with high-risk prostate cancer should be independent of radiation regimens used. When utilizing extreme dose escalation with combination EBRT plus brachytherapy for high-risk patients, either HDR or LDR, a minimum of 12 months of ADT should be considered. However, emerging data (3) suggests truncated course of 6 months may be safe for select high-risk patients, especially those preferentially seeking to avoid sequelae of longer-term ADT. Still, more prospective data is warranted before a 6-month ADT regimen becomes routinely supported for high-risk patients undergoing combination EBRT and brachytherapy. For unfavorable intermediate-risk patients, a standard duration of 4-6 months of ADT is recommended. Ongoing and future studies testing relugolix, a novel oral gonadotropin-releasing hormone antagonist with faster testosterone recovery time, in lieu of leuprolide, or intensified regimens of ADT with second-generation androgen signaling inhibitors may impact future recommendations of ADT duration with extreme dose escalated EBRT plus brachytherapy.

KQ7: What are strategies for improving toxicity and quality of life following HDR implant?

RTOG 0321 was a landmark multi-institutional trial establishing the safety and efficacy of combination EBRT 45 Gy with HDR brachytherapy 19 Gy in 2 fractions (single implant) for localized prostate cancer. At 10 years the rate of late Grade 3 GI and GU adverse events was 4% and 5%, respectively (27). Notably, this was a prospective cohort that included patients from 14 different institutions, and no single institution was allowed to contribute more than 20 patients. The low toxicity rate provides reassurance that adherence to high-quality HDR implants can be generalizable and achieved across multiple institutions.

Genitourinary structures

A dosimetric analysis of RTOG 0321 showed positive correlations with acute grade 2+ GU adverse events with higher urethral dose at multiple levels, most significantly at V120. There was a negative association with acute grade 2+ GU adverse events and homogeneity index. For late toxicities (median follow-up time of 2.5 years), there were positive correlations with grade 2+ GU adverse events at multiple urethral dose levels, especially V110. There were also positive correlations with PTV high dose volumes (i.e., hot spots) and implanted volume. This work, as well as many others, suggests that the dose-limiting structure in brachytherapy is the urethra (unlike EBRT where it is

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Table 7
Range of HDR brachytherapy boost (15 Gy x 1) planning constraints currently in use.

	GEC-ESTRO	Crook J et al	NRG GU 009	ASCENDE	Suggested
CTV V100	>95% (14.3 Gy)	≥98%	≥95% (14.3 Gy)	≥90% (13.5 Gy)	>95%
CTV V125		55-65%			
CTV V150	≤40% (6 Gy)		<35% (5.25 Gy)	≤40% (6 Gy)	≤35–40%
CTV V200			<15% (2.25 Gy)	≤14% (2.1 Gy)	≤15%
CTV D90	>100% (15 Gy)			>100% (15 Gy)	>100%
Rectum	D2cc ≤10 Gy	D1cc ≤9.5 Gy	V75% <1 cc (11.25 Gy) Dmax ≤100% (15 Gy)	V75% <1 cc (11.25 Gy) Dmax ≤100% (15 Gy)	V75% <1 cc Dmax ≤100%
Bladder			V75%(cc) ≤1 cc (11.25 Gy) D0.1cc(%) ≤113% (16.95 Gy)	Dmax ≤100% (15 Gy) V75% <1 cc (11.25 Gy)	V75% <1 cc Dmax ≤100%
Urethra	D10 ≤17 Gy D30 ≤15 Gy	Dmax 115% (17.25 Gy)	V125% (cc) ≤1 cc (18.75 Gy) V150% (cc) ≤0 cc (22.5 Gy)	Dmax ≤120% (18 Gy) D10 ≤115% (17.25 Gy)	Dmax ≤115-120% D10≤115%

the rectum) (56–61). However, it remains unclear what the ideal urethral dose constraint is and whether constraints should be modified for certain patient risk factors, such as high baseline urinary symptoms. The bladder, namely bladder neck which is challenging to define on imaging, is also an organ-at-risk during HDR brachytherapy planning, but a clear correlation between bladder dose and clinical toxicities has not been established. In fact, bladder dosimetry is not routinely evaluated with transrectal ultrasound (US) based planning. In Table 7, commonly used protocol-directed constraints for HDR brachytherapy planning are listed. Two protocols (GEC-ESTRO and Crook et al. (18)) – which predominantly utilize US-based planning – do not include a bladder constraint at all.

It is important to note that for LDR brachytherapy, dose to the bladder neck is correlated with incidence of GU toxicity (62). Yet, this correlation has not been reproduced in patients treated with HDR brachytherapy (63). Similarly, dose to the external urethral sphincter (EUS) has been significantly associated with incidence of GU toxicity in patients receiving LDR brachytherapy (64); however, this association has not been seen with HDR brachytherapy. This does not imply that the bladder neck and/or EUS are not important avoidance structures with HDR brachytherapy, as robust dosimetric analysis in large datasets in this population is lacking. As such, it is essential that accurate delineation of the prostate base and apex is conducted to avoid excessive dose deposition within the bladder neck and/or external urinary sphincter. For patients undergoing CT-guided planning, prostate fiducial placement at the base and apex, respectively, may help delineate the prostate borders for contouring. Further, brachytherapists are encouraged to contour these GU substructures, which may facilitate future analyses to measure any association between bladder neck and/or EUS dose with GU toxicity following HDR brachytherapy. A recent consensus for delineating GU substructures, including bladder neck and EUS, at the time of prostate treatment planning were recently published and can be used as a guide (65).

Similar challenges are arising with emerging data in nonbrachytherapy cohorts regarding the association of urethral dose and GU toxicity. For example, in the FLAME trial, which utilized intraprostatic microboosting, a urethra planning directive of D0.1 cc of ≤80 Gy was used, which provided equivalent toxicity outcomes with microboosting compared with standard EBRT (66). Further, data from prostate stereotactic body radiotherapy (SBRT) and hypofractionation studies also suggest an association between maximal urethral dose and cumulative incidence of grade 2+ late urinary toxicity, where the risk rises steeply above urethral 75-80 Gy EQD2 (67). Meanwhile, a typical combination regimen of 45 Gy EBRT plus HDR brachytherapy 15 Gy x 1 results in a urethral EQD2 of 97 Gy (assuming an alpha/beta of 3). Whether stricter urethral planning directives, based on patients treated with hypofractionated EBRT or SBRT, should be adapted to HDR brachytherapy directives is unknown. Additionally, there will soon be longer term toxicity outcomes with "HDR-like" SBRT boost and SBRT monotherapy dosing; whether any associations between organs-at-risk dose and GU toxicity will be relevant for HDR brachytherapy planning remains to be seen.

Gastrointestinal structures

The incidence of acute and/or late bowel toxicity after HDR brachytherapy boost is very low with existing constraints, as shown in Table 7. For example, in RTOG

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0321, which used 3D-conformal, not IMRT, for the EBRT, there was only 1 grade 3 gastrointestinal late adverse event (proctitis), which resulted in a 10-year cumulative incidence of 4%. Whether grade 1-2 rectal toxicities, which cumulatively occurred in 24 of 115 patients in RTOG 0321, could be improved with stricter rectal wall constraints is unclear. Rectal spacers, which have been shown to improve early and late grade 1-2 rectal toxicity in patients treated with dose-escalated EBRT alone (68,69), may be utilized for patients treated with combination EBRT and HDR brachytherapy. Caution is advised in patients with larger glands, as the placement of a spacer may introduce pubic arch interference that can limit the feasibility of catheter implantation. However, whether rectal spacers significantly improve grade 1-2 bowel toxicity or patient-reported quality of life in patients treated with combination EBRT and HDR brachytherapy remains to be validated. For example, patient-reported bowel quality of life in Crook et al. (18) prospective randomized trial, which included patients receiving EBRT with brachytherapy without rectal spacer, returned to near baseline at 5 years in the HDR boost arm.

Sexual function structures

Ongoing work is being done to determine ways to improve sexual function after prostate radiation therapy (70). There are multiple structures that may be implicated in post-treatment sexual function, including the penile bulb, the proximal penile crura, neurovascular bundles, and the internal pudendal arteries. How dose to these structures impacts early and late sexual function following prostate radiation remains under investigation for now. Given that HDR brachytherapy planning can be utilized in real-time with MRI, these structures may be easily delineated during treatment planning and may be important planning directives to improve treatment-related sexual toxicity. However, there are currently no clear dose constraint recommendations for these structures with HDR brachytherapy boost.

Suggestions for brachytherapy dose constraints

The last ABS consensus on HDR brachytherapy boost demonstrated a wide range on institution-specific dose constraints for various organs at risk. Since the time of that publication, the techniques of HDR have improved, as well as our understanding of various organs at risk and their relationship with post-treatment toxicity. However, there continues to be many unanswered questions regarding ideal organ at risk constraints, and the field of prostate brachytherapy is certainly behind the type of work that has been achieved in cervical cancer, such as with the EMBRACE-1 study (71). To provide sufficient guidance for HDR brachytherapy boost treatment planning, Table 7 summarizes the dose constraints that are being used or recommended from other consensus statements (GEC-ESTRO) (72), recently completed randomized controlled trials (Crook J et al.) (4), or ongoing randomized controlled trials (NRG GU009, ASCENDE-SBRT). The most obvious difference between currently used constraints shown in the table is that most are written as a percentage of the prescribed dose and not in terms of an absolute dose (e.g., V75% <1 cc). The exception to this is the GEC-ESTRO recommendations, which do list constraints based on an EQD2: Rectum D2cc $\leq$75 Gy EQD2, Urethra D10% $\leq$120 Gy EQD2, Urethra D30% $\leq$105 Gy EQD2. A summary of the currently used constraints is listed in the table with absolute doses for an example of a 15 Gy single fraction boost. The final column in the table provides suggested constraints that 1 can utilize in clinic. Given the variation in what is clinically acceptable, providers should use their judgement in determining which constraints to follow. However, it is recommended that constraints that are within the range of what is listed in the table be utilized.

KQ8: How are HDR brachytherapy plans evaluated?

Prostate HDR brachytherapy dose planning requires accurate target and organs at risk delineation, as well as optimal needle reconstructions. Treatment plans are created and evaluated after intraoperative transperineal catheter insertion, either with use of transrectal US, pelvic computed tomography (CT), or pelvic magnetic resonance imaging (MRI). Each of these imaging modalities can be appropriate with respective advantages/disadvantages of each (Table 8). The use of 1 versus the other may be determined by the provider and the resources available in the clinic. Notably, treatment planning must be performed on a commissioned system with source-specific documentation and quality assurance measures, as per recommendations by the American Association of Physicists in Medicine (AAPM) Task Group 53 (73). Three-dimensional dose calculations must be performed, and dose-volume analysis of target volume and organs-at-risk should be undertaken for each patient.

Historically, the most utilized imaging techniques for treatment planning are US and CT. US-based planning allows for intraoperative planning and delivery of treatment seamlessly while the patient remains under anesthesia, which can enhance cost-effectiveness and patient satisfaction (74). Additionally, as US-based planning can occur immediately in the OR after needle implantation, the patient can remain immobile in dorsal lithotomy without the need for transport out of the procedure suite, which minimizes the risk of needle displacement. This is an important advantage, as needle migration requires adjustments to be made prior to treatment planning and delivery, which would need to be done while the patient is awake with CT- or MRI-based planning and may require pain medication for needle advancement. However, the challenge of US-based planning is optimal visualization of the prostate gland and inserted needles (especially needle tips), particu-

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Table 8
Comparison of US-, CT- and MRI-based treatment planning for HDR brachytherapy.

	US	CT	MRI
Workflow	***(<2 hours)	**(3–4 hours)	*(4–5 hours)
Patient transport	***(none)	*(necessary, dependent on distance from OR to CT) **(can be limited if CT in procedure room)	*(necessary, dependent on distance from OR to MRI) **(can be limited if MRI in procedure room)
Needle migration	***(minimal)	**(at risk with patient transport) **(can be limited in CT in procedure room)	**(at risk with patient transport) **(can be limited if MRI in procedure room)
Infrastructure costs	*(Prolonged anesthesia support if using GA, longer OR time during intraoperative planning and delivery, shielded OR for HDR delivery)*	***(minimal additional costs if CT simulation available)	*(MRI access/time, specialized MRI template and needle markers)
Patient satisfaction	***(±GA throughout procedure and needle/template removal)	*(awake for ± needle adjustment, needle/template removal; prolonged immobility with interstitial catheters)	*(awake for ± needle adjustment, needle/template removal; prolonged immobility with interstitial catheters)
Identifying needle tip^	*	***	**(enhanced with MRI compatible markers)
Prostate contouring	**	*	***
OAR contouring	**	**	***

GA = general anesthesia.
*Measuring needle protrusion distance from the template or relative needle protrustion to a well-visualized needle tip can mitigate uncertainty (90).
**Least optimal.
***Optimal.
^ Measuring needle protrusion distance from the template or relative needle protrusion to a well-visualized needle tip can mitigate uncertainty (90).

larly the anterior needles, due to limited US image resolution and ultrasonic shadows from the implanted needles. Of note, contemporary techniques of utilizing needle protrusion length from the template has been shown to improve needle tip reconstruction (90). Additionally, US-based intraoperative planning and delivery requires a shielded operating/procedure room, which may be unavailable for many facilities.

CT-based planning, on the other hand, allows for rapid needle identification and reconstruction and is readily available in radiation oncology clinics. However, CT images provide suboptimal prostate gland delineation due to poorer soft-tissue contrast, especially at the prostate apex. MRI may provide optimal solutions to both prostate gland delineation and needle visualization (75,76); for example, the spatial resolution of MRI enhances the ability to delineate the prostate apex versus the external urethra sphincter, as well as facilitate contouring of a dominant intraprostatic lesion (DIL) for adequate coverage or dose escalation. However, this imaging technique is time-, cost- and resource-intensive. Additionally, if direct MRI planning is desired (as opposed to fusion with planning CT), special MR-compatible equipment (e.g. template) are required. Additionally, catheter tips can be challenging to delineate on MRI, so specialized markers may be needed for catheter reconstruction for treatment planning (77).

KQ9: What is the optimal sequencing of HDR brachytherapy with EBRT?

The HDR brachytherapy boost can be delivered either before or after EBRT. Further, the sequencing of HDR brachytherapy and EBRT does not seem to significantly impact toxicity or patient-reported outcomes. The THEPCA trial (78) was a randomized trial of men with intermediate- and high-risk prostate cancer comparing HDR brachytherapy 15 Gy in 1 fraction either before ($n = 50$) versus after ($n = 50$) EBRT 46 Gy in 23 fractions to the prostate, seminal vesicles, and pelvic lymph nodes. With a median follow-up of approximately 5 years, there was no difference in acute or late grade 1–2 genitourinary or gastrointestinal toxicities; notably, there was no grade 3+ toxicity. Additionally, there was no difference in patient-reported quality of life between arms. No statistically significant difference in disease free survival has been observed after 5 years.

KQ10: What is an appropriate EBRT dose/fractionation regimen to use in combination with HDR brachytherapy?

There is a range of EBRT dose and fractionation schemes that can be utilized when administered in conjunction with an HDR brachytherapy boost, including the following:

- 45-50.4 Gy in 1.8-2 Gy fractions (prostate ± seminal vesicles ± pelvic lymph nodes);
- 37.5 Gy in 2.5 Gy fractions (prostate ± seminal vesicles only)

When used in combination with HDR brachytherapy of 15 Gy x 1 or 10.5-11 Gy x 2, each of the above EBRT regimens will achieve the recommended overall BED >260 Gy.

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Decisions regarding which dose and fractionation to utilize may depend on multiple factors, including target volumes (i.e., prostate/seminal vesicles ± pelvic lymph nodes), patient access/amenability to protracted courses, or toxicity concerns with more hypofractionated regimens.

The most widely used EBRT regimen is conventional fractionation of ~ 45 Gy in 1.8–2.0 Gy fractions, similar to that utilized in the ASCENDE-RT trial establishing the role of combination EBRT to whole pelvis plus brachytherapy. RTOG 0321 trial, which prospectively established safety (i.e., very low grade 3 toxicity) and efficacy of combination EBRT with HDR brachytherapy for intermediate and high risk prostate cancer, also utilized 45 Gy in 25 fractions. Morton and colleagues conducted a phase II trial to test a more hypofractionated regimen of a single HDR 15 Gy in combination with EBRT 37.5 Gy in 15 fractions targeting the prostate/seminal vesicles only (34). Late grade 3 toxicity was low at 4%, and clinical efficacy/toxicity were similar as the previously used regimen of EBRT 45 Gy in 25 fractions with an HDR brachytherapy boost of 10 Gy x 2. This study established safety and efficacy with this moderate hypofractionated EBRT regimen in combination with HDR brachytherapy, when treating the prostate ± seminal vesicles only.

The PIVOTALboost trial (79) is an ongoing phase 3 randomized trial for patients with intermediate and high-risk prostate cancer in the UK that is comparing prostate only versus whole pelvis radiation, as well as with versus without HDR brachytherapy. Notably, the whole pelvis treatment regimen is 42 Gy in 20 fractions. This trial may support in the future a hypofractionated regimen to use in patients requiring elective pelvic lymph node treatment in combination with a brachytherapy boost.

With advancements in image-guidance, reproducible patient immobilization, and use of rectal spacers, there has been growing interest in ultrahypofractionated EBRT in combination with a brachytherapy boost for intermediate and high-risk prostate cancer. While the use of prostate SBRT alone has become a standard of care, the use of ultrahypofractionation to the prostate/seminal vesicles ± pelvic lymph nodes in combination with a brachytherapy boost is still limited, and long-term toxicity associated with this strategy is limited. Gorovets et al. (80) evaluated a cohort of patients from Memorial Sloan Kettering Cancer Center with localized prostate cancer receiving HDR brachytherapy 15 Gy x 1 followed by EBRT 25 Gy in 5 fractions (to the prostate ± seminal vesicles ± pelvic lymph nodes). After a median follow-up 24 months, no grade 3+ toxicities were reported. Acute and late grade 2 GI toxicity was only 1%, while acute and late grade 2 GU toxicity was 5.9% and 9.9%, respectively. Inclusion of pelvic lymph nodes and absence of rectal spacer were significantly associated with more frequent grade 1+ GU toxicity.

A phase I/II Canadian trial (81) prospectively enrolled 28 patients with intermediate-risk prostate cancer and treated EBRT 25 Gy in 5 fractions (to the prostate and proximal 1 cm of seminal vesicles using volumetric arc therapy), followed by a single HDR brachytherapy implant of 15 Gy. After a median follow-up of 4 years, toxicity results were compared with historical control groups treated with EBRT 36 Gy in 12 fractions or 37.5 Gy in 15 fractions followed by HDR brachytherapy 15 Gy x 1. Patient-reported urinary outcomes (IPSS scores) did not differ significantly between the treatment regimens. While there was a trend toward greater exacerbation of urinary symptoms with the ultrahypofractionated regimen, this difference was not statistically significant. There were no significant differences in patient-reported GU and GI toxicity, as measured by EPIC, between ultrahypofractionation and moderate hypofractionated. However, sexual toxicity, measured via EPIC, was more impacted with ultrahypofractionation as soon as 6 months and up to 24 months after treatment completion.

The HOPE trial (NCT04197141) is an ongoing Canadian phase II randomized trial comparing 45 Gy in 25 fractions versus 25 Gy in 5 fractions whole pelvis EBRT in combination with HDR brachytherapy 15 Gy x 1 in patients with unfavorable intermediate- or high-risk prostate cancer, with the primary endpoint of late bowel toxicity and quality of life. Early results after a median follow-up of 1.34 years have shown no significant differences in acute grade 2+ GU or GI toxicity. For GU toxicity, there was a 17.9% versus 9.8% rate of grade 2 toxicity between conventional and ultrahypofractionated treatment, respectively; no grade 3 GU toxicity has been reported. For GI toxicity, there was a 2.6% versus 4.9% rate of grade 2 toxicity between conventional and ultrahypofractionated treatment, respectively; there was a 4.9% rate of grade 3 GI toxicity in the ultrahypofractionated arm, and no grade 3 events in the conventionally fractionated arm (82). The PCS-XI trial (NCT05820633) is a larger ongoing Canadian phase III, noninferiority randomized trial comparing 25 Gy in 5 fractions versus 4-5 weeks of fractionated whole pelvis EBRT in combination with HDR brachytherapy 15 Gy x 1 in patients with intermediate- or high-risk prostate cancer, with primary endpoint of patient-reported and physician-graded toxicity.

The short-term toxicity profile of ultrahypofractionated EBRT with HDR brachytherapy appears reassuring; more mature toxicity and efficacy data will validate the long-term safety of this regimen, especially when treating the pelvic lymph nodes in patients at higher risk of occult lymph node metastases. Ultrahypofractionated whole pelvis is currently being prospectively evaluated in the phase III NRG GU013 trial, which is randomizing men with high-risk prostate cancer to 5-fraction SBRT versus moderate/conventionally fractionated EBRT. Treatment of the prostate with or without pelvic lymph nodes is at the discretion of the treatment provider; for those patients randomized to SBRT and receiving pelvic lymph node treatment, a dose of 25 Gy in 5 fractions is uti-

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Table 9
Target and organ-at-risk constraints with conventional and moderate hypofractionated EBRT regimens in combination with HDR brachytherapy.

	37.5 Gy in 15 fractions (Morton et al. [8])	45 Gy in 25 fractions* (Emory)
CTV	V37.5 Gy ≥99%	V45 Gy ≥99%
PTV	V35.6 Gy ≥99%	V45 Gy ≥95%
	V39.4 Gy <1%	
Rectum	V33 Gy <20%	V45 Gy <10%
	V29 Gy <35%	V35 Gy <20%
	V24 Gy <50%	V25 Gy <50%
Bladder	V29 Gy <35%	V45 Gy <15%
		V40 Gy <25%
		V30 Gy <50%
Femoral heads	V24 Gy <5%	V25 Gy <10%
Bowel bag		V45 Gy <150 cc
		V35 Gy <250 cc
Small bowel	Dmax <39.38 Gy	
Large bowel	Dmax <39.38 Gy	
Penile bulb		V25 Gy <50%

[a] Commonly used constraints but not prospectively validated.

lized. Of note, brachytherapy boost is not allowed in this trial.

While results of these ongoing trials remain to mature, it may be prudent to utilize more protracted EBRT regimens, especially when covering the pelvic lymph nodes. Nonetheless, data for 25 Gy in 5 fractions is promising, and this regimen mitigates cost and patient travel burden. While this regimen may be appropriate for experienced high-volume centers, long-term follow-up data from prospective trials will be needed for widespread uptake. Suggestions for planning constraints when using standard fractionation to 45 Gy or moderate hypofractionated 37.5 Gy in 15 fractions in combination with HDR brachytherapy are shown in Table 9.

KQ11: Which patients are suitable candidates for HDR brachytherapy boost?

Overall, patients pursuing combination EBRT plus brachytherapy should have a life expectancy such that the biochemical control advantages of a brachytherapy boost will be most likely to translate to significant advantages in long-term outcomes (e.g., lower risk of salvage ADT and/or possibly reduced risk of distant metastasis). Suitability criteria for HDR brachytherapy boost mirror that of LDR brachytherapy, with perhaps more flexibility given implantation of hollow catheters and inverse treatment planning, which facilitates dose modulation and encompassing extra-prostatic extension and seminal vesicle invasion, where seed migration concerns with LDR may be relevant. Pubic arch interference, especially for larger prostate glands, can be assessed by transrectal US, CT, and/or MRI volume study. Experienced practitioners may consider brachytherapy for patients with larger prostate glands (>60–80 cc), a limited median lobe, or prior history of transurethral resection of the prostate (TURP). While HDR brachytherapy may be appropriate in these cases, these patients may be at higher risk of acute urinary retention or acute/late GU toxicity (83,84). If a median lobe resection with a limited TURP is performed prior to brachytherapy, it is suggested to wait approximately 3 months prior to initiating treatment and use preimplant imaging to ensure there is sufficient prostatic tissue remaining that will allow appropriate catheter implantation (85). Studies have suggested that the risk of severe toxicity with HDR brachytherapy for patients with large prostate glands >60 cc is relatively low (86).

Additionally, patients pursuing an HDR brachytherapy boost should have nonsevere baseline lower urinary tract symptoms. Patient-reported outcomes, such as the international prostate symptom score (IPSS), should be utilized for quantifying baseline urinary function. Additionally, postvoid residual volume, which can be easily measured in the clinic, can be used to assess voiding function. Patients with higher baseline IPSS scores, such as >15–18, or elevated postvoid residuals, such as >100 cc, may be at greater risk of acute urinary issues following implantation (87,88). However, the risk of significant urinary toxicity with HDR brachytherapy for patients with elevated baseline urinary function may still be acceptable (89). Nonetheless, for patients with elevated baseline urinary symptoms and/or postvoid residual, medications for improving urinary function, such as alpha-blockers or antimuscarinic agents, should be considered to optimize urinary function prior to the starting treatment. A balanced conversation with the patient regarding the risks, benefits, and alternatives to a brachytherapy boost should also be clearly discussed.

Relative contraindications for any prostate brachytherapy, including HDR, include inability to tolerate general, spinal, or local anesthesia in the dorsal lithotomy position, absence of a rectum (although, a CT/MRI-guided approach is feasible but technically very challenging), rectal pathology (e.g., active fistula), or unacceptable operative

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risks (e.g., anticoagulant dependency, elevated bleeding risk).

Discussion

Intensified radiation therapy with extreme dose escalation, which can be safely achieved with combination EBRT plus brachytherapy, can provide benefits in long-term outcomes in patients with intermediate and high-risk prostate cancer. The landmark ASCENDE-RT trial utilized an LDR/permanent seed approach; however, past and emerging data suggest that HDR brachytherapy may have technical and toxicity advantages in this setting. As such, this consensus statement is intended to provide a comprehensive update on the role of HDR brachytherapy in combination with EBRT for localized intermediate and high-risk prostate cancer. Additionally, this review provides guidance on implementing HDR brachytherapy boost into clinical practice, including details on patient suitability, appropriate HDR brachytherapy and EBRT dose/fractionation schedules, image guidance options for catheter implantation and treatment planning, role of ADT, and acute/late toxicity risks that may be expected after combination treatment.

Recommendations have been guided by available randomized controlled trials or prospective studies. Yet, there remain several clinical questions surrounding combination EBRT plus HDR brachytherapy that need to be addressed with ongoing and future prospective studies. For example, in the era of ultrahypofractionation, which can enhance cost-effectiveness and patient satisfaction, larger studies with long-term follow-up are needed to establish whether 5-fraction EBRT, delivered to the prostate/seminal vesicles alone or with pelvic lymph nodes, is safe and effective, especially in men at high risk of occult lymph node metastases. Additionally, how ultrahypofractionated SBRT, which achieves a higher biological equivalent dose compared with fractionated EBRT, compares with combination EBRT plus brachytherapy is unknown and will be answered via the CCTG-PR24 ASCENDE-SBRT trial (NCT06235697). Second, focal intraprostatic boost (i.e., microboost) has been established as an isotoxic technique that can improve biochemical control in patients with intermediate and high-risk prostate cancer (22). Utilization of this technique has risen since 2021, but whether oncologic outcomes with this approach are comparable with combination EBRT with brachytherapy remains unclear and needs to be rigorously evaluated. Additionally, HDR brachytherapy, with inverse planning technique, may allow intraprostatic focal boosting without compromising toxicity. Trials utilizing HDR brachytherapy boost with image-guided intraprostatic boosting would help determine whether clinical outcomes can be further enhanced with this treatment. Third, the role and duration of ADT in the combination EBRT plus brachytherapy setting remains unclear; pooled analyses and recent smaller trials have suggested that shorter courses of ADT may be appropriate in this setting. However, larger, noninferiority trials are needed to validate the safety of shorter durations of ADT, especially in men with high-risk disease. Furthermore, second-generation androgen signaling inhibitors, such as abiraterone acetate or apalutamide, are actively being tested in the localized setting; the optimal duration of intensified ADT, especially if used with combination EBRT plus brachytherapy, will need to be evaluated in future trials. Finally, in the era of precision medicine with increased utilization of advanced imaging (e.g., PSMA PET/CT, MRI), genomic classifiers and/or histopathologic AI-based biomarkers, improved risk stratification and identification of patients at highest risk of recurrence, who may benefit the most from combination EBRT with a brachytherapy boost, will help improve patient selection and enhance long-term outcomes in this disease. Still, combination EBRT with HDR brachytherapy, particularly with high-quality implants using modern imaging and treatment planning techniques, provides a highly effective regimen with excellent quality-of-life outcomes that can be readily utilized for patients with intermediate and high-risk prostate cancer.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.brachy.2025.06.005.

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