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The current state of randomized clinical trial evidence for prostate brachytherapy

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Abstract

Interstitial brachytherapy is one of several curative therapeutic options for the treatment of localized prostate cancer. In this review, we summarize all available randomized data to support the optimal use of prostate brachytherapy. Evidence from completed randomized controlled trials is the focus of this review with a presentation also of important ongoing trials. Gaps in knowledge are identified where future investigation may be fruitful with intent to inspire well-designed prospective studies with standardized treatment that focuses on improving oncological outcomes, reducing morbidity, or maintaining quality of life. © 2019 Elsevier Inc. All rights reserved.

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1. Introduction

Interstitial brachytherapy for the treatment of localized prostate cancer began in 1917 with the first transperineal implant of radium needles [1]. More than 50 years later, dynamic transrectal ultrasound scanning laid the groundwork for modern treatment [2]. In parallel, mega-voltage external beam radiotherapy (EBRT) as a prostate cancer treatment emerged beginning in the 1960s [3]. As brachytherapy and EBRT techniques evolved, the global radiation oncology community embraced the randomized controlled trial (RCT) to scientifically test new treatment approaches. More than 40,000 men with localized prostate cancer enrolled in such trials, the majority of which used EBRT as the backbone of local curative-intent treatment. Despite its long history, brachytherapy was delivered to <5% of men on these RCTs.

Current estimates suggest <10% of patients in the United States receive brachytherapy as part of prostate cancer treatment with decreasing usage over time in both academic and community settings [4–6]. Many factors contribute to this decline, including differential reimbursement, insufficient training and experience, and the development of shorter courses of EBRT such as moderate and

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ultra-hypofractionation [7,8]. One factor not commonly discussed is knowledge gaps in the level 1 evidence to define the optimal use of brachytherapy. In what follows, we describe the considerable heterogeneity of RCT evidence to support brachytherapy with respect to prescription dose, dose rate, isotope, supplemental EBRT dose and fractionation, and the variable use and duration of androgen deprivation therapy (ADT). These issues confound our understanding of brachytherapy outcomes relative to alternative local treatments, but also provide the opportunity for the international radiation oncology community to come together to conduct well-designed, sufficiently powered RCTs to inform best practices and to advance the science.

Recent reviews of low and high dose-rate brachytherapy for the treatment of prostate cancer have been published with excellent in-depth discussions of patient selection, technical considerations, and thorough summaries of retrospective single-institution experiences [9–11]. In this review, we examine the RCT data that support the optimal use of brachytherapy. We discuss the trials to date, provide summary of important ongoing trials, and highlight opportunities and challenges for the future.

2. Methods

Clinical trials were identified using www.clinicaltrials.gov and www.isrctn.com with controlled vocabulary searches of "prostate cancer" and "brachytherapy". Medline via Pubmed was searched using the same controlled vocabulary with the clinical trials filter. Furthermore, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), Society of Urologic Oncology (SUO), and American Brachytherapy Society (ABS) guidelines were searched for brachytherapy clinical trials [12–17].

Brachytherapy was defined as either low dose-rate (LDR) (<2 Gy/h) which involves permanent implantation of iodine-125 (125I), palladium-103 (103Pd), or cesium-131 seeds (131Cs), or high dose-rate (HDR) (>12 Gy/h) which typically involves temporary placement of catheter needles and treatment with iridium-192 (192Ir).

We identified and included randomized phase II or III trials with target accrual goals of at least 100 participants with intermediate- or high-risk disease per NCCN risk grouping. In situations where trials with intermediate or high-risk disease were limited, trials with low-risk patients are discussed. Brachytherapy as focal therapy for low-risk disease is excluded from the main discussion as NCCN, ASCO, ASTRO, and SUO consensus guidelines favor active surveillance for these men. Trials evaluating symptom management medications were excluded, as were small ($n < 100$ patients) trials on loose versus stranded seeds and seed activity rates. To synthesize the evidence, the data was dichotomized into favorable risk disease (low- and favorable intermediate-risk by NCCN) and unfavorable risk disease (unfavorable intermediate- and high-risk by NCCN) whenever possible. As almost no trial reported to date provided the more recent Memorial-Sloan Kettering substratification definition of favorable and unfavorable intermediate-risk, inclusion criteria were used to generalize the classification of each trial [18]. No randomized data was identified for the use of salvage brachytherapy. We therefore include a review of select prospective, but non-randomized data for salvage brachytherapy for locally recurrent disease following previous EBRT.

3. Results

3.1 Favorable risk disease

For men with low- and favorable intermediate-risk disease, a single modality approach with brachytherapy alone is recommended based on level 1 data [12]. Several historical brachytherapy trials enrolled men with low- and intermediate-risk disease. The largest trial comparisons in this group involve brachytherapy compared with brachytherapy plus EBRT, the latter often referred to as "combination therapy". There are also several small, underpowered surgical trials comparing brachytherapy to radical prostatectomy (RP) which will be discussed first.

3.1.1 Brachytherapy vs. radical prostatectomy

The RCT evidence comparing brachytherapy to RP is limited to predominantly low-risk disease. Prior efforts to randomize patients in a multi-institutional setting have been unsuccessful [19]. The largest of these, the American College of Surgeons Oncology Group RCT of Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT), closed after 2 years due to poor accrual [20]. The 31 center trial only enrolled 56 men in 2 years out of a target goal of 1980, and is thus uninformative. One Italian single center RCT enrolled 200 men with low-risk disease and randomized them between RP and LDR brachytherapy [21]. Although prostate cancer-specific mortality (PCSM) and overall survival (OS) were not reported, biochemical control of approximately 90% in each arm was comparable with a mean follow up of 68 months. Early urinary incontinence and sexual function was worse in the RP arm, urinary irritation was worse in the LDR arm, and urinary stricture rates and patient reported function and bother were similar. A Cochrane review from 2011 reported this trial at high risk of bias given disease-free survival was not reported using standard methods, and no intention-to-treat analysis was performed [22]. Since the Cochrane report, the same Italian group repeated its RP vs. LDR RCT in low-risk men ($n = 165$), this time with a robot-assisted RP, with similar findings with 2 years of follow up [23]. Lennernas et al. also reported a Swedish RCT in 2015 that compared RP to HDR brachytherapy (20 Gy in 10 Gy per fraction) plus EBRT (50 Gy in 2 Gy fractions). Only 89 of

the goal of 360 men with localized prostate cancer were enrolled from 1996 to 2001. Though significantly underpowered, there were no discernable differences in post-treatment health-related quality of life (QOL) between surgery and brachytherapy combined with EBRT [24].

In summary, these trials were largely unable to reach the accrual goal required for meaningful analyses, investigated primarily low-risk patients (in whom such immediate treatment is not endorsed), and thus do not provide sufficiently robust findings to adequately inform treatment decisions. Hence, it remains largely unknown whether brachytherapy or RP provides superior disease control or better QOL.

3.1.2 Brachytherapy vs. brachytherapy and external beam radiotherapy

Merrick et al. completed 2 consecutive RCTs comparing brachytherapy to brachytherapy with supplemental EBRT. The earlier of the 2 trials (referred to as 44/20) was completed between 1999 and 2004. Brachytherapy was delivered using 103Pd (115 Gy) and patients were randomized to either a 44 Gy or 20 Gy supplemental EBRT. Over 500 men were enrolled, but due to administrative case censoring at the Puget Sound Veterans Administration Hospital (neither ethical nor scientific reasons), long-term data was available in only 247 patients. Patients with predominantly intermediate-risk were enrolled, but approximately 15% in each arm had high-risk disease. Median follow up was 11.3 years, one of the longest follow-up durations of any brachytherapy trial [25]. At 13-year follow-up there were no significant differences in biochemical failure (8.2% vs. 8.0%), PCSM (4.0% vs. 1.0%), or overall mortality (42.8% vs. 40.3%) for the 44 Gy, and 20 Gy arms, respectively. This level 1 data does not support the current guideline recommendations for ≥44 Gy of supplemental EBRT combined with brachytherapy [16].

The second RCT (20/0) was completed between 2004 and 2013. Men were randomized to either 103Pd (115 Gy) brachytherapy with 20 Gy supplemental EBRT or 103Pd brachytherapy alone (125 Gy) [25]. This cohort included more favorable risk men; all had T1c-T2b disease, and nearly all had serum prostate-specific antigen (PSA) <10 ng/mL (93%) and Gleason score 7 (94%) (although grouping of 3 + 4 vs. 4 + 3 was not reported). Due to the same administrative case censoring, outcomes were available for 383 of the 471 enrollees. At the 5-year median follow-up, there was no significant difference in biochemical failure (21% [brachytherapy with EBRT] vs. 16% [brachytherapy alone]). No prostate cancer-attributed deaths were reported, and OS was not significantly different between groups. When combining the results of the 44/20 and 20/0 trials, there was an increased risk of urethral strictures in the 44 Gy boost arm (12.2% vs. 3.2%–4.7%) compared to lower dose EBRT or no EBRT. Brachytherapy bulbomembranous urethral dose was associated with stricture rate on multivariable analysis [26].

The Radiation Therapy Oncology Group (RTOG) reported a RCT (RTOG 0232) comparing brachytherapy alone (125I to 145 Gy or 103Pd to 125 Gy) versus brachytherapy (125I to 110 Gy or 103Pd to 100 Gy) with 45 Gy EBRT [27]. This trial has been presented in abstract only, and the complete reporting is still pending. From 2003 to 2012, the trial enrolled 579 eligible patients with clinical T1c-T2b classification and a single intermediate-risk factor of a target accrual goal of 1520. Around 443 patients had a minimum follow-up duration of 5 years for interim analysis, which was declared futile to observe a between-group difference after the fifth such analysis. Progression-free survival was similar in both arms (86% vs. 85% in the brachytherapy and combination therapy arms respectively, hazard ratio [HR] 1.02). Adverse effects were higher in the combination therapy arm including increased late grade 3+ toxicity (12% vs. 7%, $P = 0.039$) with significantly lower patient-reported QOL in patients randomized to combination therapy.

When viewing these trials together, LDR brachytherapy without supplemental EBRT for intermediate-risk disease achieves similar tumor control and survival with less toxicity and better QOL than combination therapy. However, guidelines recommend the use of supplemental EBRT for unfavorable intermediate-risk, despite absence of level 1 data to substantiate this recommendation. Randomized phase II or III trials incorporating HDR have not been reported but are ongoing as discussed below.

3.1.3 Low-dose rate isotopes

The average energies for the 3 common isotopes used for LDR brachytherapy are similar (28.4 keV [125I], 20.7 keV [103Pd], and 30.4 keV [131Cs]). The half-life for decay is different; 125I (59.4 days) is longer than either 103Pd (17 days), or 131Cs (9.7 days). RCTs comparing isotopes are limited. 125I was the first isotope introduced into modern clinical brachytherapy practice in the 1960s, and it remains the most commonly used today [28]. Wallner et al. randomized 126 men with low-risk prostate cancer to either with 125I (144 Gy) or 103Pd (125 Gy) [29]. At the median follow up of 3 years, biochemical control was equivalent, but, again, in a population most suited to active surveillance [30]. Early urinary toxicity was more pronounced with 103Pd but resolved by 6 months [31].

In summary, there is no level 1 data to support preferential selection of a particular isotope for the treatment of intermediate- or high-risk prostate cancer with LDR brachytherapy (Table 1).

3.1.4 Low-dose rate vs. high-dose-rate

Feasibility reports of HDR brachytherapy for the treatment of prostate cancer were published in the early 1990s [32,33]. The advent of HDR provided several theoretical benefits. First, tumor control may be improved based on radiobiologic estimates of tumor sensitivity to increasing

Table 1
Randomized clinical trials involving brachytherapy reported to date

	n	Risk group	Arm 1	Arm 2	Median follow up	Primary endpoint	Conclusion/Comments
Brachytherapy vs. radical prostatectomy							
Surgery against brachytherapy – a randomised evaluation (SABRE-1) pilot	4 (Goal 400)	Low and intermediate	RP	103Pd (125 Gy) or 125I (145-160 Gy)	Not reported	Feasibility (not feasible)	400 planned for decision aid (DA) 30/200 eligible randomized to DA 4/30 were randomized to surgery or brachytherapy
ACSOG surgical prostatectomy versus interstitial radiation intervention trial (SPIRIT)	56 (Goal 1,980)	Low	RP	103Pd or 125I	Not reported	Overall survival (not feasible)	<10% were randomized
Italian single center (Giberti 2009, 2017)	200	Low	RP	125I	5 yr	Overall Survival (not reported)	Cochrane review of this trial reported high risk of bias in 2009 report
Swedish HDR trial (Lennernas)	89 (Goal 360)	All	RP	HDR, 192Ir 20 Gy in 2 fractions + EBRT 50 Gy in 25 fractions	2 yr	"Patient reported outcomes"	Under accrued, goal was 360 men Gleason not reported
Total	349	>75% were low risk		Variable use of dose, dose rate, and isotope	Short follow up		Randomized trials in predominately low risk patients have been unsuccessful to enroll and complete long-term follow up. Superiority or equivalence of brachytherapy to RP is unknown.
Brachytherapy +/- EBRT							
Merrick 44 Gy vs. 20 Gy EBRT boost	247	15% High 85% Intermediate	103Pd (115 Gy) + 44 Gy EBRT	103Pd (115 Gy) + 20 Gy EBRT	11.3 yr	Biochemical Control (no difference)	Variable use and duration of ADT. Powered (n = 344) to detect a 15% difference
Merrick 20 Gy vs. 0 Gy EBRT boost	383	Intermediate	103Pd (115 Gy) + 20 Gy EBRT	103Pd (125 Gy)	5 yr	Biochemical control (no difference)	Variable use and duration of ADT Powered (n = 344) to detect a 15% difference
RTOG 0232	443	Intermediate	125I (110 Gy) or 103Pd (100 Gy) + 45 Gy EBRT	103Pd (125 Gy) or 125I (145 Gy)	6.7 yr	5-yr failure free progression (no difference)	Variable isotope used
Total	1073	>95% intermediate risk	All LDR, variable isotopes used and variable LDR dose of 103Pd used.		Moderate to long-term follow up		Randomized trials in intermediate (favorable and unfavorable) risk patients have established no benefit but increased toxicity from supplemental EBRT.

(*continued on next page*)

Table 1 (***Continued***)

	n	Risk group	Arm 1	Arm 2	Median follow up	Primary endpoint	Conclusion/Comments
Isotope							
Seattle trial	126 (Goal 600)	Low	125I (144 Gy)	103Pd (125 Gy)	3 yr	BCR (no difference)	
Total	126	All low risk			Short follow up		One randomized trial in low risk disease was unsuccessful to enroll and complete long-term follow up. Optimal isotope is unknown.
HDR fractionation							
Sunnybrook trial	170	23% Low 77% Intermediate	HDR, 192Ir 27 Gy in 2 fractions	HDR, 192Ir 19 Gy in 1 fraction	3.5 yr	12 mo quality of life (better with 1 fraction)	8/87 (9%) patients in 19 Gy arm had local failure
Total	170	>75% intermediate risk disease			Short follow up		One randomized trial has been reported to date on the optimal HDR dose/fraction regimen. Optimal HDR dose/fraction for monotherapy and combination therapy remains unknown.
EBRT +/- Brachytherapy							
Ontario trial	104 (goal 150)	60% High 40% Intermediate	EBRT 66 Gy in 33 fractions	HDR, 192Ir over 48 hr to 35 Gy + EBRT 40 Gy in 20 fractions	14 yr	bRFS (23% improvement)	No ADT in either arm. Stopped early as 66 Gy alone was insufficient for int and high risk
Hoskin et al.	218	54% High 42% Intermediate	EBRT 55 Gy in 20 fractions	HDR, 192Ir in 2 fractions of 8.5 Gy + EBRT 35375 Gy in 13 fractions	7 yr	bRFS (18% improvement)	Variable ADT use. Heterogenous population. EPIC 26 or comparable QOL scales not collected
ASCENDE-RT	398	70% High 30% Intermediate	EBRT 78 Gy in 39 fractions	LDR, 125I to 115 Gy + EBRT 46 Gy in 23 fractions	6.5 yr	bRFS (11% improvement)	Inadequate timing and duration of ADT for control arm
Total	720	Mixture of intermediate and high risk	All had different doses and dose/fx of EBRT	Variable brachy dose, dose rate, EBRT dose, and ADT use and duration	Moderate to long-term follow up	All BCR primary endpoints	Randomized trials in intermediate and high risk patients have established a BCR benefit at the expense of increase in severe toxicity from brachytherapy boost.

Abbreviations: ADT = androgen deprivation; bRFS = biochemical relapse free survival; EBRT = external beam radiotherapy; EPIC = Expanded Prostate Cancer Index Composite; Gy = gray; HDR = high dose rate; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LDR = low dose rate; RP = radical prostatectomy.

fraction size (known as a low alpha/beta ratio) [34]. Second, HDR catheter placement prior to source application allows for a degree of dynamic dose adjustment to optimize the balance between high target dose coverage and low surrounding normal organ dose [35,36]. Third, the capability to place catheters outside the prostate to treat extraprostatic extension of disease without possible isotope migration [10]. Nevertheless, despite these theoretical advantages, there is no level 1 data presently reported to guide preferential selection of HDR vs. LDR, or vice versa.

However, there are several ongoing trials (Table 2). The largest ($n = 232$), led by the Canadian Cancer Trials Group (CCTG, NCT02960087), randomizes men with favorable intermediate-risk disease to either LDR (125I 144 Gy) or HDR (192Ir 19 Gy in 1 fraction with boost to gross tumor volume) with a primary outcome of biochemical control at 4-year. The simultaneous integrated boost to the tumor volume in the single fraction HDR arm is based on local recurrence patterns as discussed subsequently. A Hungarian group is sponsoring a smaller (NCT02258087, $n = 100$), similarly designed trial. In contrast, the British Columbia Cancer Agency (BCCA) is sponsoring a randomized comparison (NCT02692105, initially $n = 60$, recently expanded to 200 patients) of a 2 fraction HDR regimen (27 Gy in 2 fractions, 1–2 weeks apart) to LDR (125I 144Gy) with urinary domain-related QOL as primary outcome.

In summary, no level 1 data have been reported to date to support the optimal brachytherapy method (HDR vs. LDR) for the treatment of prostate cancer. Trials to address this question are ongoing.

3.1.5 High-dose-rate fractionation

Historical single-institution HDR series are heterogeneous. Most included various treatment schedules from 4 to 9 fractions [10]. Two fractionation regimens were developed over time based on consecutive nonrandomized prospective studies [37,38]. Limiting HDR monotherapy to a single fraction has been an area of interest to further increase convenience and reduce costs [39–41]. There is now randomized data with short-term follow-up comparing 2 fractions to one. The Sunnybrook group reported early (median follow-up 20 months) toxicity and patterns of failure data from their randomized phase II trial comparing 27 Gy deliver over 2 fractions to 19 Gy in 1 fraction ($n = 170$). Both regimens had low rates of grade 3 toxicity (<1%). The 1-year patient reported urinary outcomes favored the single fraction arm [42]. However, local failure was higher in the single fractionation arm (8 patients vs. 1 patient), and all failures occurred within initial gross tumor volume [43].

Given the historical heterogeneity in fractionation schemes that have been reported, and the absence of mature results of studies directly comparing treatment schedules, there remains limited level 1 data to support the optimal dose and fractionation regimen for HDR monotherapy.

3.2 Unfavorable risk disease

Unfavorable intermediate- and high-risk disease most often requires multi-modality treatment. Brachytherapy has been evaluated in several randomized trials, predominantly as a brachytherapy boost combined with EBRT.

3.2.1 Brachytherapy vs. brachytherapy and EBRT

The randomized data for brachytherapy monotherapy in those with unfavorable risk disease is limited. The 44/20 trial by Merrick et al. included patients with unfavorable risk disease. Sixteen percent had Gleason 8-10 and 15% had PSA >10 ng/mL [25]. The 20/0 trial also included a small number of unfavorable risk men; 2% had Gleason 8-10 and 7% had PSA >10 ng/mL. However, both trials are confounded by the heterogeneous use and duration of ADT (approximately 30% and 8%, respectively), which impacts biochemical control with brachytherapy[44], and leads to challenges interpreting results.

Although brachytherapy alone is the most evidence-based strategy for favorable risk disease, the benefit of supplemental EBRT for unfavorable intermediate- or high-risk disease is unclear. Despite the lack of randomized evidence, guidelines recommend combination brachytherapy with EBRT over brachytherapy monotherapy for this patient population [12,16]. RCTs are needed in this area to further clarify the optimal role of supplemental EBRT.

3.2.2 EBRT vs. EBRT with brachytherapy

Two RCTs have been conducted to compare low-dose EBRT alone to EBRT with a brachytherapy boost. These trials are potentially better positioned to show improvements in outcomes given the low-dose of EBRT used in the control arm at the time. A third trial used modern dose-escalated EBRT as its control arm.

The first study ($n = 104$) from Ontario, Canada compared 66 Gy in 33 EBRT fractions to 40 Gy EBRT in 20 fractions with a 35 Gy 192Ir boost delivered over 48 hours (equivalent to 84 Gy delivered in conventional 2Gy/day fractions or EQD2) [45]. This trial has reported at 14 years median follow-up, with only 5 patients lost to follow-up [46]. Approximately 60% of men had at least one high-risk feature; 39% had clinical T3 disease and 36% had PSA >20 ng/mL. In the long-term update, 72% of patients had died, thus providing long-term outcomes. The trial did not allow concurrent use of ADT and provides a nonconfounded interpretation of the benefit of dose escalation with a brachytherapy boost. The primary outcome was a composite of biochemical failure, clinical failure or PCSM. Despite enrolling only 70% of its target accrual of 150 patients, the primary outcome was met with 47% experiencing failure in the combination group and 70% in the low-dose conventional EBRT group (HR 0.53; 95% confidence interval [CI] 0.31–0.88). No significant differences were noted in metastasis (HR 0.70, 95%

Table 2
Ongoing randomized trials

	Sponsor	Trial type	n	Opened	Randomization (Treatment for single arm)	Primary endpoint
Favorable risk disease						
Brachytherapy monotherapy LDR vs. HDR						
NCT02692105	British Columbia Cancer Agency	Phase III RCT with pilot	200 [1]	May-16	- HDR (2 fraction treatment) - LDR	36-mo EPIC urinary domain
NCT02960087 (CCTG PR19)	Canadian Cancer Trials Group	Phase II RCT	232	Nov-16	- HDR (192IR 19 Gy/1 fraction with boost to GTV) - LDR (125I 144 Gy)	PSA <0.4 ng/ml at 48 mo
NCT02258087 (PROMOBRA)	National Institute of Oncology, Hungary	RCT	100	Sep-14	- HDR (192IR 19 Gy/1 fraction) - LDR (125I 145 Gy)	Acute and late toxicity (CTCAE)
Unfavorable risk disease						
EBRT +/- Brachytherapy						
NCT02271659 (GETUGP05)	Hospices Civils de Lyon	Phase III RCT	298	Jun-13	- EBRT 46 Gy prostate/SV with 80 Gy boost - EBRT 46 Gy prostate/SV + LDR (110 Gy) or HDR (14 Gy) boost - *also includes favorable intermediate risk men*	5-yr bPFS
NCT02303327 (PCS VI)	Jewish General Hospital Montreal Quebec	Phase III RCT	296	Jan-15	- 68 Gy/25 fx + 28 mo ADT - 46 Gy / 23 fx + 15-Gy HDR boost + 28 mo ADT	Acute and late toxicity
Brachytherapy boost LDR vs. HDR						
NCT01936883 (BrachyQOL)	British Columbia Cancer Agency	RCT	200	Jan-14	46 Gy in 23 fractions followed by LDR 125I 115 Gy 192Ir 15 HDR followed by 46 Gy in 23 fractions	IPSS, IIEF, EPIC
Brachytherapy +/- ADT						
UMIN000003992 (SHIP 36B)	Kanazawa University Graduate School of Medical Science, Japan	Phase III	340	Apr-01	Neoadjuvant 6 mo ADT + I125 LDR + supplemental EBRT plus or minus 24 mo adjuvant ADT	bPFS
NCT00664456 (SHIP 0804)	Translational Research Center for Medical Innovation, Kobe, Hyogo, Japan	Phase III	421	Apr-08	Neoadjuvant 3 mo ADT + I125 LDR plus or minus 9 mo adjuvant ADT - *also includes favorable intermediate risk disease*	10 yr bPFS
Treatment timing						
NCT02618161 (THEPCA)	Southend University Hospital Foundation NHS Trust	RCT	100	Sep-17	Randomizes sequence of EBRT and HDR: -46 Gy in 23 fractions first, then HDR -15 Gy HDR first, then EBRT	Grade 3−4 GU Toxicity
All trial "Active" per ClinicalTrials.gov on 09/21/2018						

Abbreviations: ADT = androgen deprivation; bPFS = biochemical progression free survival; EBRT = external beam radiotherapy; EPIC = Expanded Prostate Cancer Index Composite; GU = genitourinary; Gy = gray; HDR = high dose rate; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LDR = low dose rate; PSA = prostate specific antigen; RCT = randomized clinical trial.

[1] Expanded to 200 patients after accrual of 60 men over 18 mo in pilot study.

CI 0.32–1.57) or PCSM (HR 0.79, 95% CI 0.34–1.87). There was a 50% reduction (27% absolute) in the use of salvage ADT with combination therapy ($P = 0.007$), but long-term quality of life data associated with subsequent therapy was not collected. Severe late toxicity was approximately 3-fold nonsignificantly higher in the combination arm (15.7% vs. 5.7%, $P = 0.12$), a reflection of severe late GU toxicity (13.7% vs. 3.8%, $P = 0.09$).

A second trial ($n = 218$) completed between 1997 and 2015 compared low-dose EBRT to combination brachytherapy with HDR [44]. Dose and fractionation differed from that of the Ontario group. Patients were randomized to low-dose EBRT of 55 Gy in 20 fractions (EQD2 64–66 Gy) or to 35.75 Gy in 13 EBRT fractions with 2 fraction boost with 192Ir HDR of 8.5 Gy per fraction (total EQD2 92 Gy). This was an equivalent to approximately 26 Gy dose escalation in 2 Gy fractions. Most patients had either intermediate-risk (42%) or high-risk (54%) disease. ADT was not uniformly administered, but 60% of intermediate-risk patients received ADT. At a median follow-up of 7 years, biochemical control was improved (66% vs. 48%, $P = 0.04$) without differences in metastatic progression or PCSM. Overall, there was similar late toxicity in both arms, including cumulative incidence of severe Grade 3 urinary toxicity of 30% in both arms. The 7-year incidence of surgically managed urethral strictures was higher in the combination arm (8% vs. 2%, $P = 0.10$).

The most recently reported RCT is the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) that enrolled 398 men from 2002 to 2011. Patients were randomized to 78 Gy EBRT vs. 46 Gy EBRT with a 115 Gy 125I LDR boost, and in each case ADT was to be held constant at 12-months duration (not an optimal duration based on relevant RCTs) [47–50]. EBRT was delivered in 2 Gy fractions. Although there are uncertainties converting LDR dose to EQD2, it is estimated that the combination arm delivered 90 to 95 Gy in EQD2, translating to a 12 to 17 Gy dose escalation. Clinical seminal vesicle invasion (T3b), PSA >40 ng/mL, prior TURP, and pre-ADT prostate volume >75 cc were excluded. This trial enrolled 70% high-risk and 30% intermediate-risk patients. ASCENDE-RT is unique compared to the other 2 trials in that it compared combination therapy to a more standard EBRT control arm dose at 78 Gy in 39 fractions. The primary endpoint of the ASCENDE-RT trial was to detect a biochemical progression free survival (bPFS) improvement of 15% or greater using the PSA nadir + 2 ng/mL definition.

The trial was reported after a median follow-up of 6.5 years including oncologic outcomes[51] and toxicity [52]. There was significant improvement at 7-year in bPFS with combination therapy (86% vs. 75%, $P < 0.001$), with no difference in metastasis-free survival (91% vs. 93%), prostate-cancer-specific survival (96% vs. 94%), or OS (86% vs. 82%). The bPFS difference was significant in both the intermediate-risk and high-risk patients.

ASCENDE-RT also reported treatment-related morbidity. Early grade ≥2 GU toxicity was 16% vs. 33% in the EBRT and brachytherapy boost arms, respectively. No grade ≥3 early GI toxicities occurred in either arm. At 5 years, the cumulative incidence of grade ≥3 toxicity was greater with a brachytherapy boost (18% vs. 5% $P < 0.001$), as was the 5-year prevalence (9% vs. 2%, $P = 0.058$). The 5-year cumulative incidence of late grade ≥3 GI toxicity was also higher (8% vs. 3%, $P = 0.124$). There was an increase in incontinence (pad use) in the combination arm (7% vs. 1%) and a 4-fold increase in the need for catheterization (12% vs. 3%). Severe late GI toxicity was also seen only in the combination arm, with one patient undergoing subtotal colectomy for ischemic colitis, and another who died from complications related to a recto-urethral fistula.

To date, no sufficiently sized RCTs have been reported comparing EBRT with HDR boost compared to dose-escalated EBRT. The CCTG Group recently reported results of a feasibility study (PR 15), a small 60 person trial. Patients with intermediate-risk disease were randomized to either EBRT (in either 60 Gy in 20 fractions [86%] or 78 Gy in 39 fractions [14%]) or HDR 15 Gy + 37.5 Gy in 15 EBRT fractions. There was one grade 3 GI toxicity in the EBRT arm (3%) and 2 grade 3 toxicities in the HDR boost arm (8%) [53].

In summary, the 2 earlier low-dose EBRT trials with brachytherapy boost are consistent with most EBRT dose escalation trials in that dose escalation improves biochemical control and increases toxicity, without demonstrable effect on metastasis, PCSM, or OS. However, none of the brachytherapy trials were sufficiently sized to detect a moderate effect on metastasis or survival endpoints. Each trial used a different dose and fractionation of brachytherapy as well as EBRT, thus impeding sound pooled analyses. Only ASCENDE-RT compared dose-escalated EBRT with combination EBRT and brachytherapy. The trial used an LDR boost and the control arm received inadequate duration of ADT for high-risk disease. There was a biochemical control absolute benefit of 11% at the 6.5-year median follow up at the expense of a 21% increase in late grade ≥3 toxicity. There is presently controversy as to whether such an improvement in biochemical control is clinically meaningful when it is also associated with increased toxicity [54–56].

Several ongoing trials continue to explore the role of brachytherapy boost (Table 2). GETUG P05 (NCT02271659, $n = 298$) completed accrual of intermediate-risk men randomized between dose-escalated EBRT or EBRT plus an LDR or HDR brachytherapy boost. Many of these men will have favorable risk disease. The results for men with unfavorable intermediate-risk disease will be difficult to interpret without the use of ADT, which is the standard of care with dose-escalated EBRT. In contrast, the PCS VI study (NCT02303327, $n = 296$) includes high-risk men and all received 28 months of ADT. Men with at least

one of (1) clinical T3-4 disease, (2) Gleason > 8 or (3) PSA > 20 ng/mL will be randomized between 68 Gy delivered over 25 fractions or 46 Gy in 23 fractions plus a 15 Gy HDR boost. Other ongoing trials are testing the role of a focal boost, but brachytherapy is not directly tested in the randomization. One of the largest of these studies is the PIVOTAL boost RCT from the University of Leeds (ISRCTN80146950). Nearly 2000 men will be enrolled with a 4-arm randomization including a prostate boost and the inclusion of elective pelvic nodal EBRT. If a dominant intraprostatic lesion is identified on staging magnetic resonance imaging (MRI), the role of focal boost will also be randomized. The method of boost (i.e., intensity modulated vs. HDR) will not be randomly assigned. Similarly, The Princess Margaret Cancer Centre group completed the accrual of a prospective phase 2 trial (NCT01802242, $n = 80$) in men with unfavorable intermediate-risk and an MRI-visible lesion, comparing EBRT 76Gy in 38 fractions, plus either an EBRT integrated boost (up to 95 Gy) or HDR focal boost (10 Gy in one fraction) to the dominant intraprostatic lesion.

3.2.3 Role of androgen deprivation therapy, next generation hormonal therapy, and pelvic lymph node treatment

In contrast to EBRT, the role of ADT, chemotherapy, and next-generation ADT are largely untested in combination with brachytherapy. In 2017, Keyes et al. published a systematic review of ADT with prostate brachytherapy [57]. Of the 52 selected studies, only 2 RCTs were included and these were the aforementioned 44/20 and 20/0 trials of Merrick et al., neither of which randomly assigned ADT. Two Japanese moderate-sized RCTs completed accrual and results are awaited (Table 2).

Other EBRT RCTs evaluating ADT either allowed or will allow inclusion of brachytherapy. For example, the TROG 03.04 RADAR trial randomized men to either 6 or 18 months of ADT. Several EBRT regimens were allowed (66, 70, and 74 Gy; total $n = 814$) along with a brachytherapy boost (EBRT 46Gy + HDR 19.5Gy in 3 fractions, $n = 237$) [58]. The relative benefit of long-term ADT on local progression was present even in those who received an HDR boost; however, the absolute benefit was smaller (absolute improvement of 7% at 74 Gy vs. 3% with HDR boost). Similarly, RTOG 0815 enrolled over 1,500 men to assess short-term ADT in men with intermediate-risk disease receiving dose-escalation. Patients may be selected for either an LDR or HDR boost, and treatment with brachytherapy is a stratification factor. However, there may be insufficient brachytherapy accrual to sufficiently test the effect of short-term ADT in these patients.

Several trials investigating the role of next generation hormonal agents also allow brachytherapy. This includes the Trans-Tasman Radiation Oncology Group sponsored Enzalutamide in Androgen Deprivation Therapy with Radiation Therapy for High Risk, Clinically Localized, Prostate Cancer (NCT02446444, $n = 802$) RCT, and the European Organisation for Research and Treatment of Cancer sponsored ARN-509 Apalutamide With Radiotherapy and Androgen Deprivation Therapy in Prostate Cancer (NCT03488810, $n = 990$) RCT. However, based on existing practice patterns, it is unlikely that there will be a sufficient number of patients receiving brachytherapy boost to address whether ADT improves outcomes in these men.

Similarly, no RCT presently reports outcome examining the role of elective pelvic nodal EBRT with brachytherapy. The PIVOTAL boost trial is a 2×2 randomization that may help answer this question, as may RTOG 0924, a large ($n = 2580$) RCT in intermediate- and high-risk prostate cancer. Although stratification includes either HDR or LDR boost, it remains to be seen whether a sufficient number of such patients can be accrued to allow indicative subgroup analyses.

3.3 Salvage brachytherapy

Additional local therapy after primary EBRT has historically been associated with severe toxicity, both with salvage RP [59] and salvage LDR brachytherapy [60]. In an attempt to standardize salvage brachytherapy and to rigorously assess patient outcomes, RTOG 0526 enrolled 100 men with biopsy proven local recurrence after prior EBRT, and then administered I125 (140 Gy) or 103Pd (120 Gy) as a second attempt for radiotherapeutic tumor control. Toxicity was less than assumed with combined late GI and GU grade 3 toxicity in 14% with no Grade 4 or 5 events [61].

Others investigated HDR salvage brachytherapy. In a phase II study, Yamada et al. demonstrated 5-year bPFS of 68.5% and distant metastases-free survival of 81.5% in 42 men treated with 36 Gy in 6 fractions with one grade 3 urinary incontinence [62]. Murgic et al. published their prospective experience of 15 men with 27 Gy delivered over 2 fractions to the MRI visible lesion [63]. At a median follow up of 3-year, PSA failure free rate was 61% and only one grade 3 event occurred. The same group has a pilot study (NCT02560181, $n = 30$) that opened in August 2014 which treats the whole prostate gland with HDR (10.5 Gy in 2 fractions) with an integrated boost of 13.5 Gy with each fraction to the tumor. Others are targeting the tumor only; the BCCA group in 2 HDR fractions (NCT03246802, $n = 15$), and the Loyola University group in 1 fraction up to 30 Gy (NCT03312972, $n = 24$). The Princess Margaret Cancer Centre group has an active study of MRI-guided HDR including 2 sequential arms of whole-gland with integrated boost 16Gy and 22Gy in 2 fractions, respectively) and a focal only (26Gy in 2 fractions) (NCT NCT00913939, $n = 100$). Still others are exploring the role of hyperthermia with HDR in the salvage setting including investigators at University of Erlangen-Nürnberg, (NCT03238066, $n = 77$) and Thomas Jefferson University (NCT02899221, $n = 24$).

3.4 Concluding thoughts: challenges and opportunities for the future

Brachytherapy is a cost-effective and valuable treatment option [64]. Despite this, usage has declined since its peak in 2002 by 50% from 17% to 8% overall [6]. This trend is evident for both intermediate- and high-risk disease. Although multiple factors have contributed to the decline, we believe the best strategy for reversing it is through standardizing treatment and leveraging the scientific impact of well-designed RCTs.

Well conducted RCTs with broad inclusion criteria, clinically meaningful endpoints, and adequate power and follow up provide Level 1 evidence to guide care [65]. We could not identify a fully accrued or ongoing study with a primary endpoint of distant metastasis, prostate cancer-specific or overall survival. The RCT is a powerful tool. It established norms for dose-escalated EBRT [66], short- [48,67] and long-term ADT [49,50,68], with widely disseminated penetration into commonly-used clinical practice as a consequence. Advances in brachytherapy will be best served by similar efforts. An investigative design focused on reducing the burden of symptomatic local tumor progression, distant metastasis or PCSM, or on reducing treatment-attributed toxicity or preservation of clinically meaningful quality of life domains is best positioned to change practice patterns.

We recognize that randomized trials are difficult to conduct in general, let alone when comparing a procedural versus a noninvasive treatment [69]. These trials have precedent, however, and have been successful in diseases such as cervical cancer [70], non-small cell lung cancer [71], mesothelioma [72], brain metastasis [73], spine metastasis [74], ocular melanoma [75], and laryngeal cancer [76]. The ProtecT trial is an example of randomizing surgical, non-surgical, and active monitoring treatments in prostate cancer when both EBRT and radical prostatectomy were guideline concordant [30]. Certain strategies employed in ProtecT were instrumental in its success. The investigators highlighted the importance of clearly defining the treatment arms, avoiding misinterpreted terms, and focusing on clinical equipoise [77]. Randomizing EBRT vs. brachytherapy approaches have an advantage as such comparisons are not reliant on support of other surgical specialties to discuss equipoise.

The way forward, however, begins with brachytherapy standardization. We have highlighted the significant variability in dose, isotope, and dose rate of brachytherapy used across RCTs to date. Such heterogeneity makes it challenging to know whether the higher toxicity seen with combination brachytherapy in select studies is due to brachytherapy in general, or the dose, dose rate, isotope, or technique utilized. Several trials discussed above are investigating low-dose rate vs. high-dose rate methods (NCT02692105 and NCT02960087), the optimal combination with EBRT (NCT01936883), and with ADT (NCT00664456). These trials will help to establish agreement on the most promising, reproducible approaches to advance into prospective testing versus non−brachytherapy-based treatments.

In summary, the optimal use and role of brachytherapy remains unknown given the paucity of completed randomized trials. We view this as an opportunity to usher in a new era of clinical trials to help define the optimal dose, fractionation, dose-rate, combinatorial approaches with EBRT and/or systemic therapies, and methods to minimize toxicity to achieve optimal outcomes with this powerful modality. Reliance on retrospective data is insufficient for brachytherapy to have a prominent role in the management of prostate cancer. Equipoise within the radiation oncology community is critical to randomize patients to various forms of brachytherapy, otherwise we fear brachytherapy use will continue its decline. The best way forward is with a concerted effort to standardize practice patterns, and to conduct well-designed RCTs.

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