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A Systematic Review of the Efficacy and Toxicity of Brachytherapy Boost Combined with External Beam Radiotherapy for Nonmetastatic Prostate Cancer

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Abstract

Context: The optimum use of brachytherapy (BT) combined with external beam radiotherapy (EBRT) for localised/locally advanced prostate cancer (PCa) remains uncertain.
Objective: To perform a systematic review to determine the benefits and harms of EBRT-BT.

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Evidence acquisition: Ovid MEDLINE, Embase, and EBM Reviews—Cochrane Central Register of Controlled Trials databases were systematically searched for studies published between January 1, 2000 and June 7, 2022, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Eligible studies compared low- or high-dose-rate EBRT-BT against EBRT ± androgen deprivation therapy (ADT) and/or radical prostatectomy (RP) ± postoperative radiotherapy (RP ± EBRT). The main outcomes were biochemical progression-free survival (bPFS), severe late genitourinary (GU)/gastrointestinal toxicity, metastasis-free survival (MFS), cancer-specific survival (CSS), and overall survival (OS), at/beyond 5 yr. Risk of bias was assessed and confounding assessment was performed. A meta-analysis was performed for randomised controlled trials (RCTs).

Evidence synthesis: Seventy-three studies were included (two RCTs, seven prospective studies, and 64 retrospective studies). Most studies included participants with intermediate-or high-risk PCa. Most studies, including both RCTs, used ADT with EBRT-BT. Generally, EBRT-BT was associated with improved bPFS compared with EBRT, but similar MFS, CSS, and OS. A meta-analysis of the two RCTs showed superior bPFS with EBRT-BT (estimated fixed-effect hazard ratio [HR] 0.54 [95% confidence interval {CI} 0.40–0.72], $p < 0.001$), with absolute improvements in bPFS at 5–6 yr of 4.9–16%. However, no difference was seen for MFS (HR 0.84 [95% CI 0.53–1.28], $p = 0.4$) or OS (HR 0.87 [95% CI 0.63–1.19], $p = 0.4$). Fewer studies examined RP ± EBRT. There is an increased risk of severe late GU toxicity, especially with low-dose-rate EBRT-BT, with some evidence of increased prevalence of severe GU toxicity at 5–6 yr of 6.4–7% across the two RCTs.

Conclusions: EBRT-BT can be considered for unfavourable intermediate/high-risk localised/locally advanced PCa in patients with good urinary function, although the strength of this recommendation based on the European Association of Urology guideline methodology is weak given that it is based on improvements in biochemical control.

Patient summary: We found good evidence that radiotherapy combined with brachytherapy keeps prostate cancer controlled for longer, but it could lead to worse urinary side effects than radiotherapy without brachytherapy, and its impact on cancer spread and patient survival is less clear.

1. Introduction

Primary localised/locally advanced nonmetastatic prostate cancer (PCa) may be treated by radical prostatectomy (RP), external beam radiotherapy (EBRT), brachytherapy (BT), or a combination of BT and EBRT (EBRT-BT). Radiation treatments are often combined with androgen deprivation therapy (ADT) [1].

International guidelines recommend that EBRT-BT be considered for unfavourable intermediate/high-risk PCa [1–4]. However, several questions regarding EBRT-BT remain, including how EBRT-BT compares with definitive EBRT or RP ± postoperative (adjuvant or early salvage) EBRT (RP ± EBRT) for (1) long-term biochemical control (at/beyond 5 yr), (2) clinically relevant survival endpoints (metastasis-free survival [MFS], cancer-specific survival [CSS], and overall survival [OS]), (3) long-term genitourinary (GU) and gastrointestinal (GI) toxicities, and (4) health-related quality of life (HRQoL). In addition, there remains uncertainty regarding which patients are most likely to benefit from EBRT-BT and the role of ADT. The aim of this study was to perform a systematic review to address these questions.

2. Evidence acquisition

This systematic review was undertaken by the European Association of Urology (EAU) Prostate Cancer Guideline Panel. A protocol for the study was published a priori on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/; CRD42022349278). The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Cochrane guidelines [5,6]. Databases including Ovid MEDLINE, Embase, and EBM Reviews—Cochrane Central Register of Controlled Trials were systematically searched on July 17, 2023 for articles published in English between January 1, 2000 and July 17, 2023. The search strategy and PRISMA checklist are shown in the Supplementary material.

Eligibility criteria were randomised controlled trials (RCTs) or prospective/retrospective nonrandomised comparative studies that included patients with histologically confirmed localised/locally advanced nonmetastatic PCa (cN0 M0) treated with curative intent. The index intervention was EBRT-BT performed using high-dose-rate (HDR) or low-dose-rate (LDR) BT boost. Studies using pulsed-dose-rate BT boost were excluded as it is no longer commonly used. BT monotherapy and studies where one or more treatment arms included <50 participants were also excluded. Comparator interventions were EBRT ± ADT and RP ± EBRT. The primary outcomes were biochemical control and grade 3+ late GU/GI toxicity at/beyond 5 yr. The secondary outcomes were MFS, CSS, OS, local control, and HRQoL at/beyond 5 yr. Prespecified disease and treatment-related factors of interest were clinical T stage,

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Gleason score, prostate-specific antigen (PSA), risk group, and pelvic nodal EBRT and ADT use/duration. Risk groups were identified using National Comprehensive Cancer Network (NCCN) guidelines.

Abstract and full-text screening, data extraction, risk of bias assessment (using Cochrane Risk of Bias 2 tool [5]) and evaluation of confounding factors were performed independently in duplicate (F.S., F.Z., E.C., and A.N.), and disagreement was resolved by discussion with an independent third party (T.V.D.B. and A.M.H.). Where a potential confounder was balanced across treatment arms or controlled for in the analysis, this was judged to be at a low risk of confounding. A sensitivity analysis of outcomes from retrospective studies at a low risk of confounding was performed. A Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment was performed for the two RCTs to evaluate the quality of evidence. A qualitative synthesis was primarily planned due to the anticipated clinical and methodological heterogeneity of the included studies. However, the clinical and methodological characteristics of the two included RCTs [7,8] were considered sufficiently similar to performing a fixed-effect inverse variance weighted meta-analysis of the hazard ratio (HR) for the outcomes biochemical progression-free survival (bPFS), MFS, and OS. Direct estimates of unadjusted HRs were used wherever possible and approximated using methods described by Parmar et al. [9] otherwise. RevMan software was used. A p value of <0.05 was taken to indicate a statistically significant difference between groups.

3. Evidence synthesis

3.1. Quantity of evidence identified

The study selection process is shown in Figure 1. Seventy-three studies were included [7,8,10–71]: two RCTs [7,8], seven prospective studies [24,31,40,46,47,72,73], and 64 retrospective studies [10–23,25–30,32–39,41–45,48–71,74–80]. Incorrect comparator was the most common reason for exclusion.

3.2. Risk of bias and confounding assessment

The risk of bias and confounding assessments for RCTs and prospective studies are shown in Figure 2. The two RCTs were judged to have a low risk of bias for all domains, aside from those related to blinding of participants/personnel and outcome assessment [7,8]. The seven prospective studies were judged to be at a high risk of bias [24,31,40,46,47,72,73]. Aside from the studies by Joseph et al. [31] and Lee et al. [40], these studies were also judged to be at a high risk of confounding for all domains apart from the type of BT boost [24,46,47,72,73]. The risk of bias and confounding assessments for the 64 retrospective studies are shown in the Supplementary material. All 64 retrospective studies were judged to be at a high risk of bias [10–23,25–30,32–39,41–45,48–71,74–80]. Of these, 11 studies were judged to have accounted for all five confounding domains [15,16,32–34,41,42,52,53,63,76]. Clinical T stage and Gleason score were accounted for by 51 studies, use of ADT by 39 studies, type of BT boost by 30 studies, and EBRT volume by 18 studies.

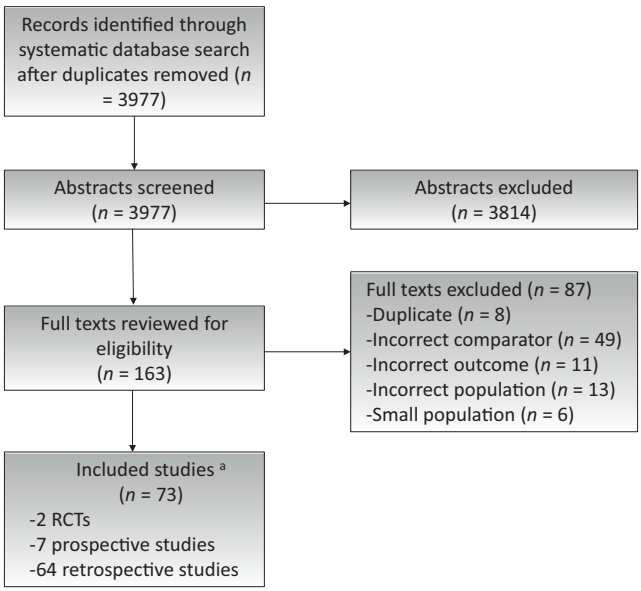

Fig. 1 – PRISMA flow chart. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT = randomised controlled trial. [a]Data from three associated publications is included with the RCT by Morris et al. [8].

3.3. Characteristics of included studies and summary of results

A summary of baseline demographic, disease, and treatment characteristics alongside the results for biochemical control and late GU/GI toxicity for the two RCTs and seven prospective studies is shown in Table 1 [24,31,40,46,47,72,73]. The results for MFS, CSS, OS and HRQoL are summarised in Table 2. Equivalent data for the 64 retrospective studies are shown in the Supplementary material [10–23,25–30,32–39,41–45,48–71,74–80].

3.3.1. Baseline patient, disease, and treatment characteristics

The two RCTs compared EBRT-BT against EBRT [7,8]. Morris et al. [8] compared LDR EBRT-BT (115 Gy LDR boost combined with 46 Gy in 23 fractions) against dose-escalated EBRT (78 Gy in 39 fractions). Eligible patients had T1-3a N0 M0 intermediate- or high-risk disease, with initial PSA <40 ng/ml. The target volume was prostate and pelvic nodes. All participants received 12 mo of ADT. Hoskin et al. [7] compared HDR EBRT-BT (17 Gy HDR boost in two fractions combined with 35.75 Gy EBRT in 15 fractions) against EBRT (55 Gy in 20 fractions). Eligible patients had T1–3 N0 M0 low-, intermediate, or high-risk disease, with PSA <50 ng/ml. The target volume was the prostate. Approximately 75% of participants received ADT (typically, 6 mo for intermediate-risk disease and 3 yr for high-risk disease). In the studies of Morris et al. [8] and Hoskin et al. [7], approximately 30% and 40% of participants had intermediate-risk disease and 70% and 55% of participants had high-risk disease, respectively.

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Fig. 2 – Risk of bias assessment for randomised controlled trials and prospective observational studies of brachytherapy combined with external beam radiotherapy. ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; HDR = high dose rate; LDR = low dose rate.

Six prospective studies compared EBRT-BT against EBRT [24,31,40,46,47,73], and one study compared it against RP ± EBRT [72]. Three studies used HDR EBRT-BT [24,31,46], three studies used LDR EBRT-BT [40,47,72], and one study used both modalities [73]. Three studies used pelvic nodal EBRT in up to 18% of participants [40,47,72]. ADT use in six studies ranged from 15% to 100% [31,40,46,47,72,73]. No participant received ADT in the study of Helou et al. [24]. The proportions of participants with intermediate- and high-risk disease in five studies ranged from 14% to 45% and 24% to 85.7%, respectively [31,40,46,47,72]. All participants in the studies of Helou et al. [24] and Krauss et al. [73] had intermediate-risk disease.

Of 64 retrospective studies, participants were treated with LDR boost in 11 studies [11,19,20,39,41,42,52–54,59,80], HDR boost in 17 studies [15,21,30,32–34,49,55,56,58,60,63,66,67,69,76,79], and both LDR and HDR boost in 11 studies [13,35–38,54,61,68,74,77,78]. In 24 studies, the type of BT boost was not recorded. The comparator arm(s) were EBRT in 41 studies [11–13,15,16,20–22,26,29,32–35,41–43,45,48,51–56,58,60,63–70,74–79], both EBRT and RP ± EBRT in 18 studies [10,14,17,18,23,25,27,28,36–39,44,50,57,61,62,71], and RP ± EBRT in five studies [19,30,49,59,80]. Pelvic nodal EBRT was used in 18 studies [13,15,20,36,38,41,42,48,49,52,53,56,58,60,61,69,76,77] and not used in ten studies [21,30,32–34,45,54,63,68,80]; in the studies where it was used, the proportion of participants who received pelvic nodal EBRT ranged from 30.6% to 100% and from 24.7% to 100% for EBRT-BT and EBRT, respectively. ADT was used in 45 studies [11–13,15,16,19–

Table 1 – Summary of baseline characteristics and primary endpoints for randomised controlled trials and prospective observational studies of brachytherapy combined with external beam radiotherapy

Study ID Design Country Recruitment period	Treatments, *n* (%) BT technique BT dose EBRT technique EBRT dose Pelvic nodes ADT (%) ADT duration RP technique pN status RP margins Postop RT	Follow up, median (IQR or range)	Age, median (IQR or range)	iPSA (ng/ml), median (IQR or range)	Gleason score (%)	cT stage (%)	Risk category (%)	Biochemical control, % (95% CI) Statistical comparison	Statistical comparison	Late GU toxicity, % (95% CI)	Statistical comparison	Late GI toxicity, % (95% CI)	Statistical comparison
Morris [8] RCT 2016 (including Rodda 2017 [88], Rodda 2017 [89], and Oh 2023 [90]) Canada 2002–2011	EBRT-BT: 200 (50.3%) LDR: 115 Gy 3dCRT: 46 Gy in 23# WPRT: 100% ADT: 100% 12 mo	6.5 yr (NR)	67 yr (range 49–84)	10.1 (range 2.4–40)	Gleason 6, 6.1% Gleason 7, 52.5% Gleason 8–10, 41.4%	T1–2, 70.2% T3a, 29.8%	NCCN: Intermediate 29.8% High 70.2%	5-yr bPFS: 88.7% (83.9–93.5) 7-yr bPFS: 86.2% (80.8–91.6) 9-yr bPFS: 83.3% (76.7–89.9) 10-yr bPFS: 85% (80–90)	5-yr HR for bPFS 2.17 (1.33–3.45), $p = 0.002$ 10-yr HR for bPFS 2.12 (1.39–3.25), $p < 0.001$	Clinician-reported 5-yr cumulative incidence Grade 3: 18.4% (12–25) Grade 4/5: 2.1% (0–6) 5-yr cumulative prevalence Grade 3: 8.6% Urethral stricture rate: 8.5% PROM-assessed 6-yr change in mean urinary function score: −3.6	5-yr cumulative incidence Grade 3: HR 3.46 (1.7–77), $p < 0.001$ Grade 4/5: HR 25 (0.19–22.6), p=0.6 Cumulative prevalence Grade 3: HR NR, $p = 0.058$ Change in mean urinary function score: $p = 0.04$	Clinician-reported 5-yr cumulative incidence Grade 3: 8.1% (3–13) Grade 4/5: 1% (NR) 5-yr cumulative prevalence Grade 3: 1% (NR) PROM-assessed 6-yr change in mean bowel function score: −3.5	5-yr cumulative incidence Grade 3: HR NR, $p = 0.12$ Change in mean urinary function score: not significant
	EBRT: 198 (49.7%) 3dCRT: 78 Gy in 39# WPRT: 100% ADT: 100% 12 mo	6.5 yr (NR)	69 yr (range 45–86)	11 (range 2.7–39.1)	Gleason 6, 5% Gleason 7, 55% Gleason 8–10, 40%	T1–2, 71.5% T3a, 28.5%	NCCN Intermediate 31.5% High 68.5%	5-yr bPFS: 83.8% (78.2–89.4) 7-yr bPFS: 75% (67.8–82.2) 9-yr bPFS: 62.4% (52.6–72.2) 10-yr bPFS: 67% (60–74)		5-yr cumulative incidence Grade 3: 5.2% (1–8) Grade 4/5: 0.6% (0–2) 5-yr cumulative prevalence Grade 3: 2.2% Urethral stricture rate: 1% PROM-assessed 6-yr change in mean urinary function score: −0.5		5-yr cumulative incidence Grade 3: 3.2% (0–6) Grade 4/5: 0% 5-yr cumulative prevalence Grade 3: 2.2% (NR) PROM-assessed 6-yr change in mean bowel function score: −2.2	
Hoskin [7] RCT 2020 UK 1997–2005	EBRT-BT: 110 (50.9%) HDR: 17 Gy in 2# 3dCRT: 35.75 Gy in 15# No WPRT ADT: 77% Low risk 3 mo: 50% Intermediate risk 6 mo: 60% High risk 3 yr: 92%	124 mo (range 8–194)	70 yr (range 47–80)	PSA <10, 32%; 10–20, 41%; >20, 27%	Gleason 6, 42%; 7, 40%; 8–10, 18%	T1–2, 69% T3, 31%	Low 2% Intermediate 44% High 54%	6-yr RFS: 71% 12-yr RFS: 48% 6-yr bPFS: 76% 12-yr bPFS: 69%	HR for RFS 0.23 (0.06–0.41), $p = 0.001$ bPFS: $p = 0.004$	6-yr estimates of severe toxicity: 30% 12-yr estimates of severe toxicity: 42% 6-yr prevalence of severe toxicity: 11% 8-yr prevalence of severe toxicity: 13% 6-yr estimates of urethral stricture: 6% 12-yr estimates of urethral stricture: 10%	EBRT-BT vs EBRT estimates of severe toxicity: $p = 0.6$ 6-yr prevalence of severe toxicity: $p = 0.05$ 8-yr prevalence of severe toxicity: $p = 0.2$ Estimates of urethral stricture: $p = 0.3$	6-yr estimates of severe toxicity: 7% 12-yr estimates of severe toxicity: 8% 6-yr prevalence of severe toxicity: 0.9% 8-yr prevalence of severe toxicity: 0%	EBRT-BT vs EBRT estimates of severe toxicity: $p = 0.9$ 6-yr prevalence of severe toxicity: $p = 1$ 8-yr prevalence of severe toxicity: $p = 0.5$
	EBRT: 106 (49.1%) 3dCRT: 55 Gy in 20# No WPRT	132 mo (range 9–206)	70 yr (47–80)	PSA <10, 34%; 10–20, 41%; >20, 25%	Gleason 6, 45%; 7, 38%; 8–10, 17%	T1–2, 77% T3,	Low 7% Intermediate 40%	6-yr RFS: 55% 12-yr RFS:		6-yr estimates of severe toxicity: 29%		6-yr estimates of severe toxicity: 6% 12-yr estimates of	

(*continued on next page*)

Table 1 (continued)

Study ID Design Country Recruitment period	Treatments, *n* (%) BT technique BT dose EBRT technique EBRT dose Pelvic nodes ADT (%) ADT duration RP technique pN status RP margins Postop RT	Follow up, median (IQR or range)	Age, median (IQR or range)	iPSA (ng/ml), median (IQR or range)	Gleason score (%)	cT stage (%)	Risk category (%)	Biochemical control, % (95% CI) Statistical comparison	Statistical comparison	Late GU toxicity, % (95% CI)	Statistical comparison	Late GI toxicity, % (95% CI)	Statistical comparison
	ADT: 75% Low risk 3 mo: 29% Intermediate risk 6 mo: 60% High risk 3 yr: 93%					23%	High 53%	27% 6-yr bPFS: 60% 12-yr bPFS: 49%		12-yr estimates of severe toxicity: 38% 6-yr prevalence of severe toxicity: 4% 8-yr prevalence of severe toxicity: 7% 6-yr estimates of urethral stricture: 3% 12-yr estimates of urethral stricture: 8%		severe toxicity: 7% 6-yr prevalence of severe toxicity: 0.8% 8-yr prevalence of severe toxicity: 1.9%	
Krauss [73] Prosp[a] 2023 USA 2009–2016	EBRT-BT: 171 (12%) LDR: 148 (10%) I-125 110 Gy or Pd-103 100 Gy HDR: 23 (2%) HDR 21 Gy in 2# 3dCRT or IMRT: 45 Gy in 25# No WPRT ADT: 50.3% Duration: 6 mo	EBRT ± BT: median 6.3 yr (range 0–10.3) EBRT + ADT: median 6.4 yr (range 0–10.2)	EBRT ± BT: <70, 63%;≥70, 37% EBRT ± BT + ADT: <70, 57%; ≥70, 43%	EBRT ± BT: ≤10, 72%; 10–20, 28% EBRT ± BT + ADT: ≤10, 71%; 10–20, 29%	EBRT ± BT: Gleason ≤3 + 3, 8%; 3 + 4, 67%; 4 + 3, 25% EBRT ± BT + ADT: Gleason ≤3 + 3, 8%; 3 + 4, 64%; 4 + 3, 28%	T1–2, 100%	Intermediate 100%	PSA failure-free rate[b] EBRT-BT vs EBRT-BT + ADT: 82.5% vs 89.8%	$p = 0.19$				
	EBRT: 1321 (88%) 3dCRT or IMRT: 79.2 Gy in 44# No WPRT ADT: 49.7% Duration: 6 mo	EBRT ± BT: median 6.3 yr (range 0–10.3) EBRT + ADT: median 6.4 yr (range 0–10.2)	EBRT ± BT: <70, 63%; ≥70, 37% EBRT ± BT + ADT: <70, 57%; ≥70, 43%	EBRT ± BT: ≤10, 72%; 10–20, 28% EBRT ± BT + ADT: ≤10, 71%; 10–20, 29%	EBRT ± BT: Gleason ≤3 + 3, 8%; 3 + 4, 67%; 4 + 3, 25% EBRT ± BT + ADT: Gleason ≤3 + 3, 8%; 3 + 4, 64%; 4 + 3, 28%	T1–2, 100%	Intermediate 100%	PSA failure-free rate[b] EBRT vs EBRT + ADT: 74.8% vs 83.5%	$p < 0.001$				
De [72] Prosp 2022 USA 2011–2012	EBRT-BT: 112 (6.8%) LDR: 100% I-125 median 91 Gy (IQR 80–110) Pd-103 median 100 Gy (IQR 92–100) IMRT: 85% Median 45 Gy (IQR 45–52.5) WPRT: 10% ADT: 16% Duration: NR	Median 73 mo (IQR 63–79)	Median 66 yr (IQR 60–71)	PSA <10, 91%; 10–20, 7%; >20, 2%	Gleason ≤6, 34%; 3 + 4, 36%; 4 + 3, 11%; ≥8, 20%	T1–2, 100%	Low 31% Intermediate 45% High 24%			EPIC-26 (100 best, 0 worst): Urinary irritative/obstructive: 5-yr median score 88 (IQR 75–94) Urinary incontinence: 5-yr median score 92 (IQR 73–100)	Urinary irritative/obstructive: adjusted mean score difference −5 (95% CI −8.7 to 1.3), $p = 0.008$ (favouring RP) Urinary incontinence: adjusted mean score difference 13.3 (95% CI 7.7–18.9), $p < 0.001$ (favouring EBRT-BT) 5-yr subgroups: Urinary bother: adjusted mean score difference 1.3 (95% CI 0.7–2.8), $p = 0.4$ Frequency: adjusted mean score difference 1.5 (95% CI 0.8–3.1), $p = 0.2$ Burning: adjusted mean score difference 4.5 (95% CI 1–20.2), $p = 0.052$ Leakage: adjusted mean score difference 0.5 (95% CI 0.2–1.4), $p = 0.19$	EPIC-26: bowel function: 5-yr median score 92 (IQR 83–100)	Bowel function: adjusted mean score difference −4 (95% CI −6.9 to 1.1), $p = 0.006$ (favouring RP) 5-yr subgroups: Bloody stools No events at 5 yr Bowel bother: adjusted mean difference 1 (95% CI 0.2–4.1), $p = 0.9$ Bowel urgency: adjusted mean difference 2.4 (95% CI 0.8–6.8), $p = 0.12$

Table 1 (continued)

Study ID Design Country Recruitment period	Treatments, *n* (%) BT technique BT dose EBRT technique EBRT dose Pelvic nodes ADT (%) ADT duration RP technique pN status RP margins Postop RT	Follow up, median (IQR or range)	Age, median (IQR or range)	iPSA (ng/ml), median (IQR or range)	Gleason score (%)	cT stage (%)	Risk category (%)	Biochemical control, % (95% CI) Statistical comparison	Statistical comparison	Late GU toxicity, % (95% CI)	Statistical comparison	Late GI toxicity, % (95% CI)	Statistical comparison
											Pad use: adjusted mean score difference 0.1 (95% CI 0.1–0.3), $p < 0.001$ (favouring EBRT-BT)		
	RP: 1553 (93.2%) Bilateral nerve sparing: 79% Unilateral nerve sparing: 12% Non–nerve sparing 9% pN status NR R status NR Postop RT NR	Median 73 mo (IQR 63–79)	Median 62 yr (IQR 57–66)	PSA <10, 89%; 10–20, 9%; >20, 3%	Gleason ≤6, 49%; 3 + 4, 30%; 4 + 3, 11%; ≥8, 10%	T1–2, 100%	Low 42% Intermediate 42% High 17%			EPIC-26: Urinary irritative/obstructive: 5-yr median score 94 (IQR 88–100) Urinary incontinence: 5-yr median score 73 (IQR 52–100)		EPIC-26: Bowel function: 5-yr median score 100 (IQR 96–100)	
Pasalic [47] Prosp 2021 USA 2011–2012	EBRT-BT: 112 (16.1%) LDR: I-125 median 90 Gy (IQR 80–110), Pd-103 median 100 Gy (IQR 92.5–100) IMRT: 85% 3dCRT: 15% Median 45 Gy (IQR 45–52.5) WPRT: 10% ADT: 16% Duration: NR	73 mo (IQR 63–78)	66 yr (IQR 60–71)	PSA <10, 91%; 10–20, 7%; >20, 2%	Gleason 6, 34%; 7, 47%; 8–10, 20%	T1–2, 100%	Low 31% Intermediate 45% High 24%				PROM-assessed 5-yr urinary irritative (MCID 5–7): mean adjusted difference −4.5 points (−8.4 to −0.5), $p = 0.026$ 5-yr urinary incontinence (MCID 6–9): mean adjusted difference −3.8 points (−9.9 to 2.2), $p = 0.2$ 5-yr moderate/big problem: urinary function: OR 3.5 (1.5–8.2), $p = 0.004$ 5-yr moderate/big problem: frequency: OR 2.6 (1.2–5.6), $p = 0.017$ 5-yr moderate/big problem: burning: OR 4.1 (0.9–18.8), $p = 0.072$ No difference for 5-yr moderate/big problem: urinary leakage or pad use		PROM-assessed 5-yr bowel function (MCID 4–6): mean adjusted difference −2.1 (−5.7 to 1.4), $p = 0.2$ No difference for 5-yr moderate/big problem: bloody stools, bowel bother, or bowel urgency
	EBRT: 583 (83.9%) IMRT: 83% 3dCRT: 17% Median 78 Gy (IQR 76–79.2) WPRT: 18% ADT: 46% Duration: NR	73 mo (IQR 63–78)	69 yr (IQR 64–74)	PSA <10, 80%; 10–20, 15%; >20, 6%	Gleason 6, 34%; 7, 49%; 8–10, 17%	T1–2, 100%	Low 29% Intermediate 46% High 25%						
Parry [46] Prosp 2020 UK 2014–2016	EBRT-BT: 756 (5.7%) HDR: 15 Gy in 1# 84.5% IMRT: 94.6% 3dCRT: 5.4% 46 Gy in 23# 44.7% 37.5 Gy in 15# 40.1% WPRT: NR ADT: 74% Duration: NR	15.6 mo (IQR 13.5–19.7)	72 yr (range 44–90)	NR	NR	NR	Intermediate 32.7% High 67.3%			PROM-assessed mean scores: irritative/obstructive 80.7 (SD 18.4) Incontinence 85.6 (SD 19.9)	Irritative/obstructive adjusted mean difference (MCID 5): −6.1 (−8.8 to −3.4), $p < 0.001$ (but MCID contained within 95% CI) Incontinence adjusted mean difference (MCID 5): −1.5 (−3.5 to 0.5), $p = 0.13$	PROM-assessed mean scores: bowel 87 (SD 17.2)	Bowel adjusted mean difference (MCID 4): 1.4 (−0.7 to 3.5), $p = 0.2$
	EBRT: 12 503 (94.3%) IMRT: 94.6% 3dCRT: 5.4%	15.6 mo (IQR 13.5–19.7)	72 yr (range 44–90)	NR	NR	NR	Intermediate 32.7% High 67.3%			PROM-assessed mean scores: irritative/		PROM-assessed mean scores: bowel 85.9 (SD	

(*continued on next page*)

Table 1 (continued)

Study ID Design Country Recruitment period	Treatments, *n* (%) BT technique BT dose EBRT technique EBRT dose Pelvic nodes ADT (%) ADT duration RP technique pN status RP margins Postop RT	Follow up, median (IQR or range)	Age, median (IQR or range)	iPSA (ng/ml), median (IQR or range)	Gleason score (%)	cT stage (%)	Risk category (%)	Biochemical control, % (95% CI) Statistical comparison	Statistical comparison	Late GU toxicity, % (95% CI)	Statistical comparison	Late GI toxicity, % (95% CI)	Statistical comparison
	74 Gy in 37# 64.8% 60 Gy in 20# 35.2% WPRT: NR ADT: 74% Duration: NR									obstructive 86.3 (SD 15.2) Incontinence 86.2 (SD 19.3)		18.3)	
Joseph [31] Prosp[a] 2019 Australia 2003–2007	EBRT-BT: 237 (22.5%) HDR: 19.5 Gy in 3# 3dCRT: 46 Gy in 23# No WPRT ADT: 100% 6 mo 50% 18 mo 50%	10.5 yr (IQR 8.2–11.8)	66.3 yr (IQR 60.6–71.4)	16 (IQR 9.9–26)	ISUP 1, 1.7%; 2, 18.1%; 3, 29.1%; 4, 24.9%; 5, 26.2%	T2, 35.9% T3–4, 64.1%	Intermediate 14.4% High 85.7%			Urethral stricture rate: 12.7%	Urethral stricture comparisons NR EBRT vs EBRT-BT: dysuria $p < 0.001$ (favouring EBRT)	NR	EBRT vs EBRT-BT: 3-yr rectal bleeding: OR 0.56 (NR), $p = 0.009$ (favouring EBRT-BT) 3-yr faecal urgency: OR 0.44 (NR), $p < 0.001$
	EBRT 66 Gy: 125 (11.9%) 3dCRT: 66 Gy No WPRT ADT: 100% 6 mo 50% 18 mo 50%	10.5 yr (IQR 8.2–11.8)	68.6 yr (63.3–72.8)	13.2 (IQR 8.4–23)	ISUP 1, 14.4%; 2, 39.2%; 3, 19.2%; 4, 12.8%; 5, 14.4%	T2, 75.2% T3–4, 24.8%	Intermediate 44% High 56%			Urethral stricture rate: 0.8%		NR	
	EBRT 70 Gy: 427 (40.6%) 3dCRT: 70 Gy No WPRT ADT: 100% 6 mo 50% 18 mo 50%	10.5 yr (IQR 8.2–11.8)	69.5 yr (64.2–73.3)	14 (IQR 9.3–22.5)	ISUP 1, 11.2%; 2, 36.1%; 3, 25.1%; 4, 13.4%; 5, 14.3%	T2, 72.8% T3–4, 27.2%	Intermediate 43.1% High 56.9%			Urethral stricture rate: 0.9%		NR	
	EBRT 74 Gy: 262 (24.9%) 3dCRT: 74 Gy No WPRT ADT: 100% 6 mo 50% 18 mo 50%	10.5 yr (IQR 8.2–11.8)	69.9 yr (64.5–74.2)	15.5 (IQR 9.8–27)	ISUP 1, 11.1%; 2, 36.6%; 3, 17.9%; 4, 18.3%; 5, 16%	T2, 68.3% T3–4, 31.7%	Intermediate 30.9% High 69.1%			Urethral stricture rate: 3.8%		NR	
Lee [40] Prosp 2018 USA 2011–2012	EBRT-BT: 109 (15.9%) LDR (77.1% I-125, 14.7% Pd-103) I-125 median 90 Gy (IQR 80–100) Pd-103 median 100 Gy (IQR 92.5–100) IMRT: 85% 3dCRT: 15% Median 45 Gy (IQR 45–52.5) WPRT: 10% ADT: 17% Duration: NR	NR	66 yr (IQR 60–71)	PSA <10, 91%; 10–20, 7%; >20, 2%	Gleason 6, 34%; 7, 46%; 8–10, 20%	T1–2 100%	D'Amico: Low 31% Intermediate 44% High 25%			3-yr PROM-assessed moderate/big problem: Urinary function 13% Pain/burning 9% Frequency 17% Leakage 7% Pad use 10%	Urinary function OR 1.8 (0.7–4.7), $p = 0.2$ Pain/burning OR 6.5 (1.9–21.8), $p = 0.002$ Urinary frequency OR 1.5 (0.6–2.3), $p = 0.4$ Urinary leakage OR 0.8 (0.2–3.3), $p = 0.7$ Pad use OR 1.9 (0.8–4.6), $p = 0.16$ 3-yr urinary irritative mean score difference −4.7 (−9.1 to −0.4), $p = 0.034$ Incontinence mean score difference −0.1 (−4.8 to 4.6), $p = 1$	3-yr PROM-assessed moderate/big problem: Bowel function 8% Bowel urgency 10%	Bowel function OR 1.2 (0.4–3.8), $p = 0.7$ Bowel urgency OR 1.1 (0.3–4.3), $p = 0.9$ 3-yr bowel function mean score difference −3 (−6.5 to 0.4), $p = 0.087$
	EBRT: 578 (84.1%) IMRT: 82% 3dCRT: 18% 46 Gy in 23# WPRT: 18% ADT: 100% Duration: NR		69 yr (IQR 64–73.8)	PSA <10, 79%; 10–20, 15%; >20, 6%	Gleason 6, 34%; 7, 49%; 8–10, 17%	T1–2 100%	D'Amico: Low 29% Intermediate 45% High 25%			3-yr PROM-assessed moderate/big problem: Urinary function 10% Pain/burning 2%		3-yr PROM-assessed moderate/big problem: Bowel function 6% Bowel urgency 7%	

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Table 1 (continued)

Study ID Design Country Recruitment period	Treatments, *n* (%) BT technique BT dose EBRT technique EBRT dose Pelvic nodes ADT (%) ADT duration RP technique pN status RP margins Postop RT	Follow up, median (IQR or range)	Age, median (IQR or range)	iPSA (ng/ml), median (IQR or range)	Gleason score (%)	cT stage (%)	Risk category (%)	Biochemical control, % (95% CI) Statistical comparison	Statistical comparison	Late GU toxicity, % (95% CI)	Statistical comparison	Late GI toxicity, % (95% CI)	Statistical comparison
										Frequency 14% Leakage 5% Pad use 8%			
Helou [24] Prosp 2014 Canada NR	EBRT-BT: 123 (59.4%) HDR: 15 Gy in 1# 3dCRT: 37.5 Gy in 15# No WPRT No ADT	61 mo (NR)	66 yr (range 45–79)	6.76 (range 2–18.6)	Gleason 6, 7.3% Gleason 7, 92.7%	T1–2 100%	NR	NR		PROM-assessed MCID: Urinary overall 58% Urinary function 54% Urinary bother 47% Median urinary score during follow-up 83.1 (range 43.1–97.3)	Urinary overall $p < 0.001$ Urinary function $p < 0.001$ Urinary bother $p < 0.001$	PROM-assessed MCID: Bowel overall 44% Bowel function 37% Bowel bother 39% Median bowel score during follow-up 94.4 (range 46.4–100)	Bowel overall $p = 0.2466$ Bowel function $p = 0.022$ Urinary bother $p = 0.076$
	SBRT: 84 (40.6%) IMRT: 35 Gy in 5# No WPRT ADT only for cytoreduction (NR)	51 mo (NR)	67 yr (range 48–82)	5.31 (range 0.83–9.93)	Gleason 6, 100% Gleason 7, 0%	T1–2 100%	NR	NR		PROM-assessed MCID: Urinary overall 18% Urinary function 20% Urinary bother 13% Median urinary score during follow-up 97.1 (range 66.3–97.3)		PROM-assessed MCID: Bowel overall 32% Bowel function 31% Bowel bother 25% Median bowel score during follow-up 94 (range 66.8–100)	

ADT = androgen deprivation therapy; bPFS = biochemical progression-free survival; CI = confidence interval; 3dCRT = three-dimensional conformal radiotherapy; EBRT = external beam radiotherapy; EBRT-BT = external beam radiotherapy combined with brachytherapy boost; GI = gastrointestinal; GU = genitourinary; HDR = high dose rate; HR = hazard ratio; IMRT = intensity-modulated radiotherapy; iPSA = initial prostate-specific antigen; IQR = interquartile range; ISUP = International Society for Urological Pathology; LDR = low dose rate; MCID = minimum clinically important difference; NCCN = National Comprehensive Cancer Network; NR = not recorded; OR = odds ratio; PROM = patient reported outcome measure; Prosp = prospective observational study; PSA = prostate-specific antigen; RCT = randomised controlled trial; RFS = relapse-free survival; RP = radical prostatectomy; RT = radiotherapy; SBRT = stereotactic body radiotherapy; SD = standard deviation; WPRT = whole pelvis radiotherapy.

[a] RCT, but allocation of EBRT-BT vs EBRT not randomised therefore described as prospective observational study.

[b] Note that comparisons were between EBRT-BT versus EBRT-BT + ADT and EBRT versus EBRT + ADT rather than between radiotherapy modalities.

Table 2 – Summary of secondary endpoints for randomised controlled trials and prospective observational studies of brachytherapy combined with external beam radiotherapy

Study ID Design Country Recruitment period	Metastatic control, % (95% CI)	Statistical comparison	Cancer-specific survival, % (95% CI)	Statistical comparison	Overall survival, % (95% CI)	Statistical comparison	Local recurrence, % (95% CI)	Statistical comparison	HRQoL	Statistical comparison
Morris [8] RCT 2016 (including Rodda 2017 [88], Rodda 2017 [89], and Oh 2023 [90]) Canada 2002–2011	EBRT-BT: 5-yr MFS: 93.3% (89.5–97.1) 7-yr MFS: 91% (86.4–95.6) 9-yr MFS: 88.6% (83–94.2) 10-yr MFS: 88% (83–93)	5-yr HR for MFS 0.93 (0.48–1.81), $p = 0.8$ 10-yr HR for MFS 1.2 (0.71–2.2), $p = 0.5$	5-yr CSS: 96.8% (94–99.6) 7-yr CSS: 96% (92.8–99.2) 9-yr CSS: 94.8% (90.8–98.8) 10-yr CSS: 95% (92–98)	5-yr HR for CSS 0.62 (0.24–1.60), $p = 0.3$ 10-yr HR for CSS 1.49 (0.72–38), $p = 0.3$	5-yr OS: 91.3% (86.9–95.7) 7-yr OS: 85.7% (79.9–91.5) 9-yr OS: 77.9% (69.7–86.1) 10-yr OS: 80% (74–86)	5-yr HR for OS 1.29 (0.80–28), $p = 0.3$ 10-yr HR for OS 1.13 (0.79–1.63), $p = 0.5$			6-yr change in mean physical function score: –15.3	Change in mean physical function score: $p = 0.03$
	EBRT: 5-yr MFS: 92.5% (88.5–96.5) 7-yr MFS: 92.5% (88.5–96.5) 9-yr MFS: 84.8% (77.2–92.4) 10-yr MFS: 86% (80–92)		5-yr CSS: 97.5% (95.1–99.9) 7-yr CSS: 94.1% (89.9–98.3) 9-yr CSS: 92.1% (86.5–97.7) 10-yr CSS: 92% (88–96)		5-yr OS: 88.7% (83.9–93.5) 7-yr OS: 81.5% (75.1–87.9) 9-yr OS: 73.6% (65.2–82) 10-yr OS: 75% (68–82)				6-yr change in mean physical function score: –6.9	
Hoskin [7] RCT 2020 UK 1997–2005	EBRT-BT: 6-yr MFS: 88% 12-yr MFS: 83%	$p = 0.6$			EBRT-BT: 6-yr OS: 86% 12-yr OS: 64%	$p = 0.8$			Data available only at 3 yr	
	EBRT-BT: 6-yr MFS: 90% 12-yr MFS: 76%				EBRT-BT: 6-yr OS: 88% 12-yr OS: 61%				Data available only at 3 yr	
Krauss [73] Prosp[a] 2023 USA 2009–2016	Distant metastasis-free rate[b]: EBRT-BT vs EBRT-BT + ADT: 94.9% vs 98.4%	$p < 0.001$			Deaths LDR EBRT-BT vs LDR EBRT-BT + ADT: 13.7% vs 6.7% Deaths HDR EBRT-BT vs HDR EBRT-BT + ADT: 8.3% vs 0%	LDR EBRT-BT vs LDR EBRT-BT + ADT: HR 0.31 (0.10–1), $p = 0.05$ HDR EBRT-BT vs HDR EBRT-BT + ADT: HR NR, $p = 1$				
	Distant metastasis-free rate[b]: EBRT vs EBRT + ADT: 92% vs 96.6%	$p = 0.003$			Deaths EBRT vs EBRT + ADT: 16.2% vs 14.5%	EBRT vs EBRT + ADT: EBRT HR 0.9 (0.69–1.2), $p = 0.5$				

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Table 2 (**continued**)

Study ID Design Country Recruitment period	Metastatic control, % (95% CI)	Statistical comparison	Cancer-specific survival, % (95% CI)	Statistical comparison	Overall survival, % (95% CI)	Statistical comparison	Local recurrence, % (95% CI)	Statistical comparison	HRQoL	Statistical comparison
De [72] Prosp 2022 USA 2011–2012									SF36 (100 best, 0 worst): Physical function 90 (95% CI 75–95) Emotional well-being 88 (95% CI 76–92) Energy and fatigue 70 (95% CI 60–80)	5-yr physical function adjusted mean difference –1.5 (95% CI –6.1 to 3.0), $p = 0.5$ 5-yr emotional well-being adjusted mean difference –1.5 (95% CI –5.9 to 2.8), $p = 0.5$ 5-yr energy and fatigue adjusted mean difference –2.7 (95% CI –6.9 to 1.6), $p = 0.2$
									SF36: Physical function 95 (95% CI 80–100) Emotional well-being 88 (95% CI 76–92) Energy and fatigue 75 (95% CI 60–85)	
Pasalic [47] Prosp 2021 USA 2011–2012			EBRT-BT: 5-yr CSS: 99% (97.1–100) 7-yr CSS: 97.3% (93.7–100)	$p = 0.6$	5-yr OS: 92.8% (91.2–99.4) 7 yr: 91% (85–97.4)	$p = 0.2$				No 5-yr significant adjusted mean difference in physical function, emotional well-being, or energy and fatigue
			EBRT: 5-yr CSS: 99.6% (99.1–100) 7-yr CSS: 96.9% (93.3–100)		5-yr OS: 92.8% (90.7–95) 7 yr: 84% (79.1–89.1)					
Parry [46] Prosp 2020 UK 2014–2016									EBRT-BT: mean HRQoL score 0.89 (SD 0.15)	HRQoL adjusted mean difference: 0.03 (0.02–0.04), $p < 0.001$ (favours EBRT-BT)
									EBRT: mean HRQoL score 0.84 (SD 0.19)	
Joseph [31] Prosp[a] 2019 Australia 2003–2007	EBRT-BT: 10-yr metastatic rate: 19.7% (15.5–23.8)	EBRT 70 Gy vs EBRT-BT: HR 0.68 (0.57–0.80), $p < 0.001$ EBRT 74 Gy vs EBRT-BT: HR 0.75 (0.56–11), $p = 0.06$	EBRT-BT: 10-yr CSM: 8.9%	EBRT 70 Gy vs EBRT-BT: HR 0.65 (0.51–0.82), $p < 0.001$ EBRT 74 Gy vs EBRT-BT: HR 0.75 (0.51–19), $p = 0.13$	EBRT-BT: 10-yr OM: 23%	EBRT 70 Gy vs EBRT-BT: HR 0.65 (0.51–0.82), $p < 0.001$ EBRT 74 Gy vs EBRT-BT: HR 0.69 (0.54–0.87), $p = 0.002$	EBRT-BT: 10-yr LR: 2.2%	EBRT 70 Gy vs EBRT-BT: HR 0.28 (0.19–0.40), $p < 0.001$ EBRT 74 Gy vs EBRT-BT: HR 0.29 (0.13–0.63), $p = 0.002$	EBRT-BT: 3-yr emotional functioning mean score 84.8 (82.6–87) Financial problem mean score 9.3 (7–	EBRT-BT vs EBRT 74 Gy: Emotional functioning mean scores $p < 0.01$ (favouring EBRT 74 Gy) Financial problem mean scores $p < 0.01$ (favouring EBRT 74 Gy) No differences in 3-yr global or social functioning scores

(*continued on next page*)

Table 2 (**continued**)

Study ID Design Country Recruitment period	Metastatic control, % (95% CI)	Statistical comparison	Cancer-specific survival, % (95% CI)	Statistical comparison	Overall survival, % (95% CI)	Statistical comparison	Local recurrence, % (95% CI)	Statistical comparison	HRQoL	Statistical comparison
									11.6)	
	EBRT 66 Gy: 10-yr metastatic rate: 26.1% (18.9–33.2)		EBRT 66 Gy: 10-yr CSM: 14.5%		EBRT 66 Gy: 10-yr OM: 29.9%		EBRT 66 Gy: 10-yr LR: 12.3%			
	EBRT 70 Gy: 10-yr metastatic rate: 26.7% (22.9–30.6)		EBRT 70 Gy: 10-yr CSM: 13%		EBRT 70 Gy: 10-yr OM: 36.2%		EBRT 70 Gy: 10-yr LR: 7.5%			
	EBRT 74 Gy: 10-yr metastatic rate: 24.9% (20–29.8)		EBRT 74 Gy: 10-yr CSM: 11.5%		EBRT 74 Gy: 10-yr OM: 31.3%		EBRT 74 Gy: 10-yr LR: 7.3%		3-yr emotional functioning mean score 90.6 (87.5–93.8) Financial problem mean score 4.7 (1.4–8)	
Lee [40] Prosp 2018 USA 2011–2012			3-yr CSS: 100% (100–100)	HR for CSS NR, $p = 0.6$	3-yr OS: 97% (93–100	HR for OS NR, $p = 0.3$				
			3-yr CSS: 99.5% (98.8–100)		3-yr OS: 95.3% (93.2–97.4)					
Helou [24] Prosp 2014 Canada NR										

ADT = androgen deprivation therapy; CI = confidence interval; CSS = cancer-specific survival; CSM = cancer-specific mortality; EBRT = external beam radiotherapy; EBRT-BT = external beam radiotherapy combined with brachytherapy boost; HDR = high dose rate; HR = hazard ratio; HRQoL = health-related quality of life; LDR = low dose rate; LR = local recurrence; MFS = metastasis-free survival; NR = not recorded; OM = overall mortality; OS = overall survival; Prosp = prospective observational study; RCT = randomised controlled trial; RP = radical prostatectomy; SD = standard deviation.

[a] RCT, but allocation of EBRT-BT versus EBRT or RP not randomised, therefore described as a prospective observational study.

[b] Note that comparisons were between EBRT-BT versus EBRT-BT + ADT and EBRT versus EBRT + ADT rather than between radiotherapy modalities.

22,26,30,32,34–39,41,42,45,48–50,52–54,56,58–61,63,66–70,74–80] and not used in three studies [29,33,55]; in the studies where it was used, the proportion of participants who received ADT ranged from 30.3% to 100% and from 5% to 100% for EBRT-BT and EBRT, respectively. Disease risk category was often not recorded, but participants with Gleason scores 8–10 were included in 52 studies [10,12,14–20,22,23,25,26,30,32,34–39,41–44,48,49,52–54,56–71,74–79] and clinical T3–4 disease were included in 48 studies [10,12,14–18,20,22,25,27,30,32–38,41–45,48,49,51–53,57,59–61,63–71,74–79].

3.3.2. Primary endpoints

3.3.2.1. Biochemical control

The primary endpoints for the RCTs by Morris et al. [8] and Hoskin et al. [7] were bPFS and relapse-free survival (RFS; defined as biochemical failure, clinical progression, or death), respectively. Hoskin et al. [7] included bPFS as a secondary endpoint. Both RCTs reported superior biochemical control with EBRT-BT versus EBRT [7,8]. In Morris et al.'s [8] study, 5-yr bPFS was 83.8% versus 88.7% for EBRT versus EBRT-BT (HR 2.17 [95% confidence interval {CI} 1.33–3.45], $p = 0.002$). At 10 yr, bPFS remained superior for EBRT-BT (HR 2.12 [95% CI 1.39–3.25], $p < 0.001$). In Hoskin et al.'s [7] study, 6-yr RFS was 71% versus 55% for EBRT-BT versus EBRT (HR 0.23 [95% CI 0.06–0.41], $p = 0.01$). The 12-yr estimates were 48% versus 27%. Six-year bPFS estimates were 76% versus 60% ($p = 0.004$) and 12-yr estimates were 69% versus 49%. This corresponds to absolute improvements in bPFS at 5–6 yr of 4.9-16% across the two RCTs. Pooling the bPFS results from the two RCTs in a meta-analysis gives an estimated overall fixed-effect HR of 0.54 (95% CI 0.40–0.72, $p < 0.001$), favouring EBRT-BT (see Fig. 3A) [7,8]. There was little evidence of important heterogeneity (chi-square $p = 0.5$ and $I^2 = 0\%$).

Of 64 retrospective studies, 27 reported either bPFS or biochemical recurrence rates [11,15,19–21,32–34,38,39,41,42,45,49,52–56,58,64,66–69,74,80]. Of these, 18 studies observed superior biochemical control with EBRT-BT against EBRT or RP ± EBRT [11,19–21,32–34,38,42,45,52–55,67–69,74]. This included eight studies that used HDR EBRT-BT [21,32–34,45,55,67,68], seven studies that used LDR EBRT-BT [11,19,20,42,52–54], and three studies that used both modalities [38,69,74]. One study observed superior biochemical control with EBRT compared with EBRT-BT [56]. Of the 25 studies that reported results for biochemical control, 5-yr bPFS estimates ranged from 67% to 98.9%, 44% to 94.8%, and 74.3% to 81% for EBRT-BT, EBRT, and RP ± EBRT, respectively. Five-year biochemical recurrence rates ranged from 11% to 12%, 27% to 30%, and 73.6% for EBRT-BT, EBRT, and RP ± EBRT, respectively.

In some studies including that of Hoskin et al. [7], EBRT-BT was not compared against dose-escalated EBRT. Of 18 retrospective studies that demonstrated superior biochemical control with EBRT-BT, in nine studies, the range of doses used in the comparator EBRT arm included schedules ≤72 Gy [21,32,33,45,54,67–69,74]. In one study that reported superior bPFS with EBRT, the single 10 Gy fraction HDR boost used in the comparator arm would be considered low [56].

3.3.2.2. Late GU toxicity.

Late GU toxicity was evaluated in 28 of 73 studies [7,8,11,15,17,24,27–34,40,42,45–47,54,56,58,60,61,66,67,69,72]. Of these, seven studies used patient-reported outcome measures (PROMs) [24,30,40,46,47, 61,72], 19 studies reported clinician-assessed toxicity [7,11,15,17,27–29,32–34,42,45,54,56,58,60,66,67,69], and two studies used both PROMs and clinician-assessed toxicity [8,31]. The RCT by Morris et al. [8] and six prospective studies evaluated PROMs [24,31,40,46,47,72]. In seven of eight studies that used PROMs, significantly worse late GU toxicity was reported in at least one urinary domain with EBRT-BT compared with EBRT or RP ± EBRT [8,24,30,31,40,46,47,72]. In seven of 21 studies that reported clinician-assessed toxicity, EBRT-BT was associated with significantly worse late grade 3+/severe GU toxicity than EBRT or RP ± EBRT [7,8,11,28,29,45,67]. In four studies, both lower- and higher-grade toxicity were combined and reported together (eg, grade 2+) [34,56,60,66].

In the study by Morris et al. [8], 5-yr cumulative incidence of clinician-assessed grade 3 late GU toxicity was 18.4% versus 5.2% (HR 3.46 [95% CI 1.7–7.1], $p < 0.001$) for LDR EBRT-BT versus EBRT. Grade 4/5 toxicity rates were 2.1% versus 0.6% ($p = 0.6$) and included two treatment-related deaths in the LDR EBRT-BT arm. One patient died following major pelvic surgery for Fournier gangrene, and the other died following pulmonary embolism/myocardial infarction during an admission for pelvic pain. The 5-yr cumulative prevalence of grade 3 late GU toxicity was 8.6% versus 2.2% ($p = 0.058$). Urethral stricture rate was 8.5% versus 1% (p value not reported). For PROMs, clinically and statistically significant 6-yr worsening of mean urinary function was reported with EBRT-BT versus EBRT ($p = 0.04$). In the study by Hoskin et al. [7], 6-yr actuarial incidence of severe clinician-reported toxicity was 30% versus 29% ($p = 0.6$) for HDR EBRT-BT versus EBRT. The 6-yr prevalence of severe toxicity was 11% versus 4% ($p = 0.05$) for EBRT-BT versus EBRT. The 8-yr prevalence was 13% versus 7% ($p = 0.2$). The 6-yr actuarial incidence for urethral stricture was 6% versus 3% ($p = 0.3$). Although differences across both RCTs did not meet conventional levels of statistical significance, there was some evidence of a greater prevalence of severe late GU toxicity of 6.4–7% with EBRT-BT at 5–6 yr.

In the six prospective studies, EBRT-BT was associated with significantly worse PROM-assessed late GU toxicity than EBRT by at least one study for the following domains: overall function (HDR and LDR EBRT-BT) [24,47], irritative symptoms (HDR and LDR EBRT-BT) [40,46], frequency (LDR EBRT-BT) [47], and burning (LDR EBRT-BT) [40]. No difference between EBRT-BT and EBRT was reported by any of the prospective studies for incontinence/pad use. In one prospective study, EBRT-BT was associated with significantly worse obstructive/irritative symptoms, but better incontinence rates and fewer pad use compared with RP ± EBRT [72].

3.3.2.3. Late GI toxicity.

Late GI toxicity was evaluated in 25 of 73 studies [7,8,11,15,24,28–33,40,42,45–47,54,56,58,60,61,66,67,69,72]. Of these, seven studies reported PROMs [24,30,40,46,47, 61,72], 16 studies reported clinician-assessed toxicity

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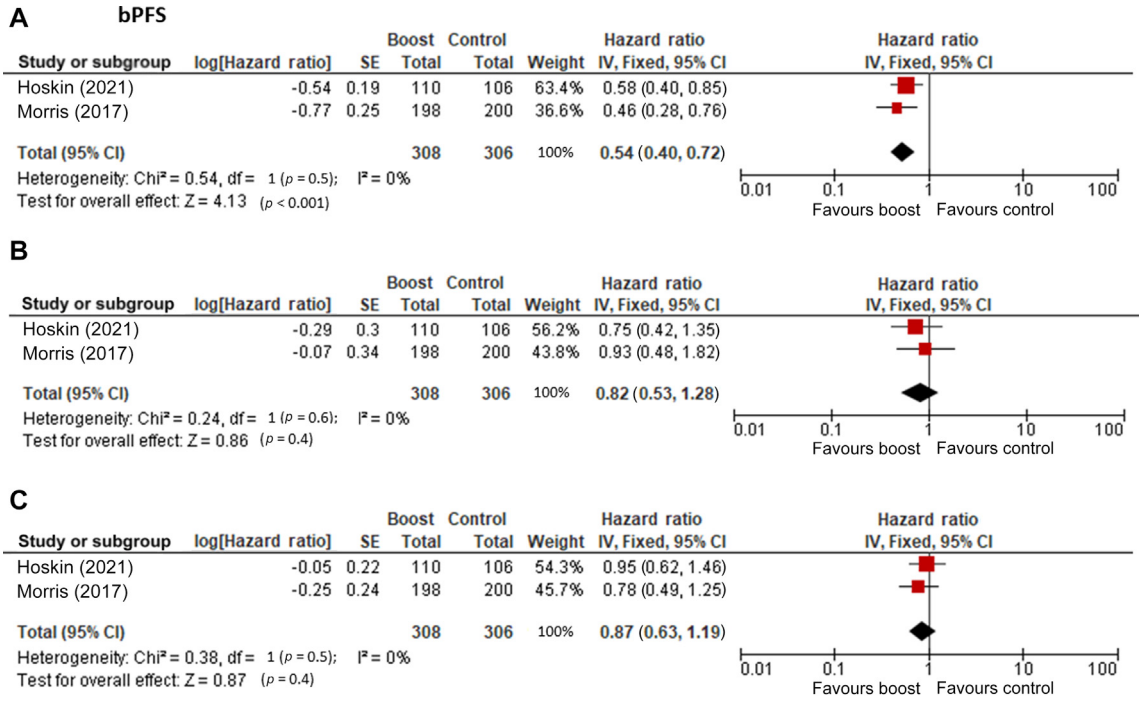

Fig. 3 – Forest plots summarising the randomised evidence for brachytherapy combined with external beam radiotherapy for the following endpoints: (A) biochemical progression-free survival, (B) metastasis-free survival, and (C) overall survival. bPFS = biochemical progression-free survival; CI = confidence interval; IV = inverse variance; MFS = metastasis-free survival; OS = overall survival; SE = standard error.

[7,11,15,28,29,32,33,42,45,54,56,58,60,66,67,69], and two studies used both PROMs and clinician-assessed toxicity [8,31]. The RCT by Morris et al. [8] and six prospective studies evaluated PROMs [24,31,40,46,47,72]. In two of eight studies that used PROMs, significantly worse late GI toxicity was reported in at least one bowel domain with EBRT compared with EBRT-BT [24,30]. In one of 19 studies that reported clinician-assessed toxicity, EBRT was associated with significantly worse late grade 3+ GI toxicity than EBRT-BT [29]. In four studies, both lower- and higher-grade toxicities were combined and reported together [11,56,60,66].

In Morris et al.'s [8] study, 5-yr cumulative incidence of clinician-assessed grade 3 late GI toxicity was 8.1% versus 3.2% ($p = 0.12$) for LDR EBRT-BT versus EBRT. Grade 4/5 toxicity rate was 1% versus 0%. The 5-yr cumulative prevalence of grade 3 late GI toxicity was 1% versus 2.2%. For PROMs, no significant 6-yr change in the mean bowel function was reported. In Hoskin et al.'s [7] study, 6-yr actuarial incidence of severe toxicity was 7% versus 6% ($p = 0.9$) for HDR EBRT-BT versus EBRT. The 6-yr prevalence of severe toxicity was 0.9% versus 0.8% ($p = 1$).

In prospective studies, no significant difference in PROM-assessed late bowel toxicity was observed between EBRT-BT and EBRT, aside from in the study of Helou et al. [24], where HDR EBRT-BT was associated with worse bowel function ($p = 0.022$). In one study, significantly worse PROM-assessed bowel function was reported with EBRT-BT than with RP ± EBRT [72].

3.3.3. Secondary endpoints

3.3.3.1. Distant metastatic control.

Distant metastatic control was reported in 26 studies [7,8,11,15,20,21,31,33,34,36–38,41,45,48,52,56,58,60,61,67–69,74,76,77]. No significant difference was reported in 5- or 10-yr MFS in the study of Morris et al. (HR 0.93 [95% CI 0.48–1.81], $p = 0.8$ vs HR 1.2 [95% CI 0.71–2.2], $p = 0.5$) [8] or 6-yr MFS in the study of Hoskin et al. (88% vs 90%, $p = 0.6$) [7] for EBRT-BT versus EBRT. Pooling the MFS results from the two RCTs in a meta-analysis gives an estimated overall fixed-effect HR of 0.82 (95% CI 0.53–1.28, $p = 0.4$), with no difference between EBRT-BT and EBRT (see Fig. 3B). There was little evidence of important heterogeneity (chi-square $p = 0.6$ and $I^2 = 0\%$).

Of prospective studies, only the study by Joseph et al. [31] evaluated distant metastatic control. HDR EBRT-BT was associated with an improvement in 10-yr distant metastatic rate versus EBRT with an equivalent dose in 2 Gy fractions (EQD2) of 70 Gy (19.7% vs 26.7%, HR 0.68 [95% CI 0.57–0.80], $p < 0.001$). No significant difference was observed when HDR EBRT-BT was compared against EBRT, which delivered an EQD2 of 74 Gy (24.9%, $p = 0.06$). Six retrospective studies observed a significant difference in distant metastatic control, all favouring EBRT-BT [20,21,36–38,76].

Twenty-three retrospective studies evaluated metastatic control [11,15,20,21,33,34,36–38,41,45,48,52,56,58,60,61,67–69,74,76,77]. The 5-yr MFS estimates were 87–100% for EBRT-BT, 73.9–100% for EBRT, and 83.1% for RP ± EBRT. The 5-yr distant metastatic rates ranged from 4.2% to 34% for EBRT-BT, 8.7% to 50% for EBRT, and 13.4% to 24% for RP ± EBRT.

3.3.3.2. PCa-specific survival.

CSS or cancer-specific mortality (CSM) was reported in 32 studies [8,10,14,20,23,25,28,31–33,36–38,40,41,43,44,47,48,51–53,57,59,62,63,65,67,68,71,74,77]. No significant difference was reported in 5- or 10-yr CSS by Morris et al. [8] for EBRT-BT versus EBRT (HR 0.62 [95% CI 0.24–1.60],

p = 0.3 vs HR 1.49 [95% CI 0.72–3.08], p = 0.3). Three prospective studies evaluated CSS or CSM [31,40,47]. Only Joseph et al. [31] observed a significant difference between HDR EBRT-BT and EBRT (10-yr CSM for EBRT-BT compared with EBRT using 70 Gy: 8.9% vs 13%, HR 0.65 [95% CI 0.51–0.82], p < 0.001). No significant difference was observed when HDR EBRT-BT was compared against EBRT using 74 Gy (p = 0.13). Twelve retrospective studies reported significantly better results with EBRT-BT than with EBRT or RP ± EBRT [10,32,36,43,51,53,57,59,62,63,65,71]. In one study, EBRT-BT was associated with improved CSS compared with EBRT but inferior CSS compared with RP ± EBRT [62].

Twenty-eight retrospective studies evaluated CSS/CSM [10,14,20,23,25,28,32,33,36–38,41,43,44,48,51–53,57,59,62,63,65,67,68,71,74,77]. The 5-yr CSS estimates ranged from 85% to 99.2% for EBRT-BT, 70.8% to 99.1% for EBRT, and 85.4% to 97.8% for RP ± EBRT. The 5-yr CSM rates ranged from 1% to 7.6% for EBRT-BT, 0% to 27% for EBRT, and 1.2% to 27% for RP ± EBRT.

3.3.3.3. *Overall survival.*

OS or overall mortality (OM) was reported in 47 studies [7,8,10,12–14,16,18,20,22,25,26,28,31–36,38,40–42,44,45,47,50,54–61,63–65,67–71,74–76,78]. No significant difference in 5- or 10-yr OS was reported for EBRT-BT versus EBRT by Morris et al. (HR 1.29 [95% CI 0.80–2.08], p = 0.3 vs HR 1.13 [95% CI 0.79–1.63], p = 0.5) [8] or 6-yr OS by Hoskin et al. (86% vs 88%, p = 0.8) [7]. Pooling the MFS results from the two RCTs in a meta-analysis gives an estimated overall fixed-effect HR of 0.87 (95% CI 0.63–1.19, p = 0.4), with no difference between EBRT-BT and EBRT (see Fig. 3C). There was little evidence of important heterogeneity (chi-square p = 0.5 and I^2 = 0%).

Three prospective studies evaluated OS or OM. Only Joseph et al. [31] observed a significant difference between EBRT-BT and EBRT. The 10-yr OM for EBRT-BT appeared superior to that for both EBRT 70 Gy (2.2% vs 7.5%, p < 0.001) and EBRT 74 Gy (7.3%, p = 0.002). Seventeen retrospective studies reported significantly better results with EBRT-BT than with EBRT or RP ± EBRT [12–14,16,20,22,25,26,32,33,35,36,42,57,59,63,65]. In one study, EBRT-BT was associated with improved OS compared with EBRT but inferior OS compared with RP ± EBRT [57].

Forty-two retrospective studies evaluated OS/OM [10,12–14,16,18,20,22,25,26,28,32–36,38,41,42,44,45,50,54–61,63–65,67–71,74–76,78]. The 5-yr OS estimates ranged from 84.7% to 100% for EBRT-BT, 54% to 100% for EBRT, and 90.3% to 96% for RP ± EBRT.

3.3.3.4. *Health-related quality of life.*

Long-term HRQoL was evaluated in six studies [8,30,31,46,47,72]. In the study by Morris et al. [8], the mean physical function score was superior with EBRT to that with EBRT-BT (p = 0.03). Three prospective studies evaluated HRQoL [31,46,47]. Parry et al. [46] observed superior adjusted mean HRQoL composite scores with HDR EBRT-BT to those with EBRT (p < 0.001). Joseph et al. [31] found superior emotional functioning mean scores and financial problem mean scores in favour of EBRT using 74 Gy compared with EBRT-BT (both p < 0.01). Pasalic et al. [47] and De et al. [72] reported no significant adjusted mean difference at 5 yr for physical functioning, emotional well-being, or energy/fatigue between EBRT-BT and EBRT and between EBRT-BT and RP ± EBRT, respectively.

3.4. *Sensitivity analysis*

Data trends in the sensitivity analysis of 11 retrospective studies at a low risk of confounding broadly mirrored those seen in the overall data [15,16,32–34,41,42,52,53,63,76]. A more detailed description is shown in the Supplementary material.

3.5. *GRADE assessment and strength of recommendation*

A GRADE assessment based on the two RCTs is summarised in Table 3. A more detailed description is shown in the Supplementary material. Based on the EAU guideline methodology, an overall strength of recommendation for EBRT-BT was defined [1]. The strength rating (either "strong" or "weak") takes into account the principles of the GRADE methodology, but is determined by a balance between desirable and undesirable consequences of treatment, the quality of available evidence (including certainty of results), as well as the impact on patient values and preferences. The strength recommendation for EBRT-BT was judged to be weak given that it is primarily based on improvements in biochemical control.

3.6. *Discussion*

This systematic review summarises the available evidence regarding the efficacy and severe late toxicity of EBRT-BT in the definitive management of localised/locally advanced PCa.

In almost all studies that evaluated biochemical control and including the two RCTs, outcomes appeared superior with EBRT-BT. Improvement in biochemical control might be an important consideration in the decision-making process for many patients. However, development of distant metastases might be a more appropriate endpoint to evaluate EBRT-BT, considering that development of metastatic disease may have a greater influence on future treatment decisions than biochemical failure alone and that MFS has been shown to be a strong surrogate for OS in PCa [81]. In contrast, biochemical recurrence after definitive radiotherapy (RT) does not appear to be strongly correlated with OS [82]. Most studies that evaluated distant metastatic control (including the two RCTs) did not observe better outcomes with EBRT-BT. This could be influenced by the presence of participants with intermediate-risk PCa within studies, who would be expected to have fewer metastatic events. The two RCTs did not find a significant difference between EBRT-BT and EBRT for either CSS or OS (possibly because, as for MFS, the studies were not powered to address these endpoints), although approximately half of the observational studies reported an improvement in these endpoints with EBRT-BT. For observational studies, differences in participant age and comorbidities could have influenced the differences observed specifically for survival endpoints. Participants who are older and/or less fit are less

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Table 3 – Summary of GRADE profile for reported outcomes for randomised controlled trials of brachytherapy combined with external beam radiotherapy

Outcome	Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty[a]
Benefits						
Biochemical control	2	Not serious	Not serious	Serious	Not serious	Moderate
Distant metastatic control	2	Not serious	Not serious	Not serious	Serious	Moderate
PCSS	1	Not serious	Serious	Not serious	Serious	Low
OS	2	Not serious	Not serious	Not serious	Serious	Moderate
Harms						
Late GU toxicity	2	Not serious	Serious	Not serious	Not serious	Moderate
Late GI toxicity	2	Not serious	Not serious	Not serious	Not serious	High
HRQoL	1	Not serious	Not serious	Not serious	Serious	Moderate

EBRT = external beam radiotherapy; EBRT-BT = external beam radiotherapy combined with brachytherapy boost; GI = gastrointestinal; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; GU = genitourinary; HRQoL = health-related quality of life; OS = overall survival; PCSS = prostate cancer–specific survival; RCT = randomised controlled trial.
[a] Strength of certainty to support difference in outcome between EBRT-BT and EBRT.

likely to be treated using invasive procedures such as EBRT-BT and RP ± EBRT, and have competing risks for survival. There is a considerable overlap in the ranges of outcomes for HDR and LDR EBRT-BT, which makes it difficult to interpret whether there could be any differences in biochemical control associated with BT modality. Fewer studies, with no RCTs and only one prospective observational study, examined RP ± EBRT, making it difficult to draw firm comparisons with EBRT-BT.

Most of the studies included participants who had NCCN intermediate- and/or high-risk PCa, meaning that the available evidence for EBRT-BT applies predominantly to patients in these risk categories. International guidelines recommend that EBRT-BT be considered for unfavourable intermediate/high-risk PCa [1–4]. Outcomes from BT monotherapy for low-risk/favourable intermediate-risk PCa in suitable patients are excellent [83,84], but for patients with unfavourable intermediate/high-risk PCa, there is a greater risk of microscopic extracapsular extension. In this scenario, EBRT-BT could be advantageous given that it may both permit dose escalation to the prostate and deliver a high dose to an appropriate target volume encompassing regions of potential microscopic disease [2].

Local failure is associated with inferior MFS, CSS, and OS, which may result from a second, later wave of distant metastatic spread [85]. Of six studies that demonstrated improved metastatic control with EBRT-BT, four predominantly included participants with high-risk PCa, including participants with Gleason 9–10 disease [20,36–38]. One interpretation of these results is that the additional dose escalation achievable using EBRT-BT could be beneficial in gaining better local control in patients with bulky and/or high-grade PCa.

Multiparametric magnetic resonance imaging and intensity-modulated RT has enabled delivery of simultaneous integrated focal EBRT dose escalation to dominant intraprostatic lesions, which is noninvasive and convenient, and may be appropriate for more patients than EBRT-BT. In the multicentre RCT FLAME study, EBRT using 77 Gy in 35 fractions with an additional focal boost up to 95 Gy was associated with improved 5-yr bPFS compared with 77 Gy in 35 fractions alone (92% vs 85%, $p < 0.001$) without an increase in late GU and GI toxicities [86]. There are also promising early results with the use of focal dose escalation using hypofractionated schedules. The phase II hypoFLAME study reported acceptable acute GU and GI toxicities (with no grade 3+ events) using 35 Gy in five fractions weekly, with a focal boost to 50 Gy [87]. It remains unclear how outcomes from EBRT with a focal boost compare against EBRT-BT.

Most studies used ADT although timing in relation to EBRT-BT and duration of use was often poorly described, meaning that it is difficult to interpret how ADT should be best combined with EBRT-BT or whether it could safely be omitted. The duration of ADT differed between the two RCTs, with 12 mo used for all participants in the study of Morris et al. [8] versus either 6 mo or 3 yr for most participants with intermediate- or high-risk PCa in the study of Hoskin et al. [7]. However, the duration of ADT appeared to be well balanced between treatment arms in each study, which suggests that this did not account for differences in outcomes between EBRT-BT and EBRT. The RTOG 0815 RCT on intermediate-risk PCa, which included nonrandomised dose escalation by either EBRT or EBRT-BT using LDR or HDR BT and randomised to 6 mo of ADT or none, observed a benefit in terms of the reduction of distant metastases for EBRT-BT with the addition of ADT [73]. The TROG 03.04 RADAR RCT on high-risk PCa, which included nonrandomised dose escalation by either EBRT or HDR EBRT-BT and randomised to either 6 or 18 mo of ADT, found that 18 mo of ADT reduced distant metastatic disease independently of the RT dose [31]. A recent analysis of the optimum duration of ADT to improve MFS for patients with high-risk PCa treated by EBRT-BT and EBRT included a multicentre retrospective cohort and participants from the RADAR and DART RCTs [79]. The optimum minimum ADT duration for EBRT-BT was calculated to be 18 mo but could possibly be less. International guidelines currently recommend that ADT use with EBRT-BT for intermediate- and high-risk disease should be in line with that used for EBRT, although the US NCCN guidelines suggest that 12 mo may be sufficient for high-risk PCa treated by EBRT-BT [1–4].

Toxicity evaluation in the two RCTs differed in the methods and timing of assessment, but LDR EBRT-BT was associated with a greater incidence of severe late GU toxicity than EBRT and included two treatment-related deaths [8]. Long-term prevalence may provide a better understanding of the impact of toxicity than incidence, which can reflect toxicity that resolves later. Although differences across the RCTs did not reach conventional levels of statistical significance,

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there was some evidence of greater prevalence of severe late GU toxicity at 5–6 yr with EBRT-BT than with EBRT [7,8]. In neither study, urinary function was a specific eligibility criterion. Prospective studies that used PROMs also observed worse late GU toxicity with EBRT-BT than with EBRT across multiple domains. Expectedly, EBRT-BT had worse irritative/obstructive but better incontinence-related symptoms than RP. The nature of retrospective studies as well as heterogeneity in terms of methods and timing of assessments limits the conclusions that can be drawn from those studies that reported toxicity outcomes. Neither RCT reported a significant difference in severe late GI toxicity, aside from some evidence of worse toxicity with LDR EBRT-BT in the study of Morris et al. [8]. Reflecting the unexpectedly severe late GU toxicity seen with LDR EBRT-BT in the study of Morris et al. [8], which included two treatment-related deaths, international guideline recommendations emphasise the importance of careful patient selection with good baseline urinary function, image guidance of BT source placement, and treatment planning and delivery of 110 Gy rather than 115 Gy LDR EBRT-BT [1,4].

Several additional limitations were identified. For the meta-analysis, direct HRs were not available for Hoskin et al. [7], and the estimates may not be accurate since these were based on only two time points. Twenty-three of 64 retrospective studies [10,12,14,16–18,22,23,25–29,43,44,50,51,57,62,64,65,70,71] were evaluations of national databases and/or included little to no treatment-related information, which limits the conclusions that can be drawn and comparisons that can be made for efficacy-related endpoints, given the potential for differences in RT technique, dose and volume, and ADT use/duration.

4. Conclusions

EBRT-BT using LDR or HDR BT is associated with superior biochemical control to EBRT, with absolute improvements in bPFS at 5–6 yr of 4.9–16% across the two RCTs. However, its impact on distant metastatic disease, CSS, and OS is less certain. Fewer studies examined RP ± EBRT, making it difficult to draw firm comparisons with EBRT-BT. Improvements in biochemical control with EBRT-BT compared with EBRT need to be weighed against the risk of severe late GU toxicity. Although differences across both RCTs did not reach conventional levels of statistical significance, there was some evidence of a greater prevalence of severe GU toxicity of 6.4–7% with EBRT-BT at 5–6 yr. There is insufficient evidence as to whether ADT can safely be omitted with EBRT-BT. This systematic review supports current guideline recommendations to consider EBRT-BT for unfavourable intermediate/high-risk PCa patients with good urinary function, although the strength of this recommendation based on EAU guideline methodology is weak given that it is primarily based on improvements in biochemical control.

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Acquisition of data: Slevin, Zattoni, Checcucci, Nacchia, Yuan, Van den Broeck, Henry.
Analysis and interpretation of data: Slevin, Zattoni, C.T. Smith, Van den Broeck, Henry.
Drafting of the manuscript: Slevin.
Critical revision of the manuscript for important intellectual content: Slevin, Zattoni, Checcucci, Cumberbatch, Nacchia, Cornford, Briers, De Meerleer, De Santis, Eberli, Gandaglia, Gillessen, Grivas, Liew, Linares Espinós, Oldenburg, Oprea-Lager, Ploussard, Rouvière, Schoots, E.J. Smith, Stranne, Tilki, C.T. Smith, Van Den Bergh, Van Oort, Wiegel, Yuan, Van den Broeck, Henry.
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Appendix A. Supplementary data

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