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Review – Prostate Cancer

Magnetic Resonance Imaging–guided Focal Boost to Intraprostatic Lesions Using External Beam Radiotherapy for Localized Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: It is anticipated that a focal boost to intraprostatic lesions (IPLs) using external beam radiotherapy (EBRT) guided by magnetic resonance imaging (MRI) will increase biochemical disease-free survival (bDFS) without increasing toxicity in the treatment of localized prostate cancer (PC).

Objective: To systematically review clinical outcomes for MRI-guided EBRT focal boost to IPLs.

Evidence acquisition: Three independent reviewers conducted literature searches in three databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. The inclusion criteria were original English-language articles from 2000 to 2021 on prospective studies of patients with localized PC ($n > 10$) receiving an MRI-guided EBRT focal boost to IPLs. The main outcomes and measures were safety, gastrointestinal (GI)/genitourinary (GU) toxicities, quality of life, and biochemical disease outcomes. Weighted random-effects meta-analyses were conducted. Heterogeneity was assessed using the I^2 statistic. Publication bias was assessed via funnel plots.

Evidence synthesis: Seventeen studies (1290 patients) were included. There were heterogeneities in patient risk category (low risk, 63; intermediate risk, 532; high risk, 695), MRI utilization, and treatment planning and delivery. All studies reported good safety, with estimated rates of 7.5%/7.0% (95% confidence interval [CI] 4.0–12.1%/2.8–12.8%) and 0.1%/0.2% (95% CI 0–0.4%/0–1.1%) for acute/late cumulative grade ≥2 and grade ≥3 gastrointestinal toxicities, and 29.5%/16.0% (95% CI 17.6–43.0%/8.3–25.7%) and 0.4%/1.3% (95% CI 0.0–1.3%/0.3–3.0%) for acute/late grade ≥2 and grade ≥3 genitourinary toxicities, respectively. Across patients in focal boost studies with follow-up >5 yr, bDFS was 92.4% (95% CI 84.5–97.7%). The overall bDFS was 95.0% (95% CI 91.9–97.4%) regardless of follow-up duration.

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Conclusions: MRI-guided EBRT focal boost to IPLs in localized PC was feasible and safe, with low GI/GU toxicities and favorable biochemical disease outcomes. Level 1 evidence supports the superior bDFS of this approach over whole-prostate irradiation for standard fractionation; however, further research is required for hypofractionation and ultra-hypofractionation.

Patient summary: We reviewed 17 studies on the use of magnetic resonance imaging (MRI)-guided radiotherapy with delivery of a higher radiation level to lesions within the prostate that were visible on MRI. This approach was well tolerated and might offer better disease control in prostate cancer over traditional radiotherapy.

1. Introduction

External beam radiation therapy (EBRT) is a well-established treatment for localized prostate cancer (PC) [1]. Studies on the dose-response relationship have shown that radiation dose escalation up to 80 Gy for the whole prostate is safe and effective in biochemical control [2–6]. Recent pathological studies of local recurrence patterns after RT suggest that the presence of intraprostatic lesions (IPLs) is a strong indicator of tumor aggressiveness, and post-RT local recurrence often originates from primary IPL sites [7–9]. Therefore, a focal dose boost to IPLs (Fig. 1) has been proposed to improve local control and increase biochemical disease-free survival (bDFS) without compromising the sparing of organs at risk (OARs) [10].

Magnetic resonance imaging (MRI), in particular multiparametric MRI (mpMRI), which mainly consists of T2-weighted (T2W) MRI, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced MRI (DCE-MRI), has been widely applied for IPL identification [11–13]. With the aid of mpMRI in RT planning, the prostate and IPLs can be better delineated and dose escalation can be more precisely prescribed to IPLs for focal boosting without increasing the dose to surrounding OARs [14–16].

Encouraging early results for focal boost to IPLs have been reported. A previous systematic review summarized 13 single-arm studies (before 2016) on focal boost to IPLs identified via MRI and other imaging modalities [17]. The efficacy and safety of focal boost using either EBRT or brachytherapy were assessed. The pooled median 5-year bDFS was estimated to be 85% (range 79–100%) [17]. With advances in mpMRI and precise image-guided RT (IGRT), increasingly more prospective studies of MRI-guided EBRT focal boost to IPLs in localized PC are being conducted, with reports of more mature clinical results.

Our aim was to better characterize the utilization, performance, and clinical value of MRI-guided focal boost to IPLs by pooling relevant prospective studies via meta-analysis to synthesize clinical evidence. We hypothesized that MRI-guided EBRT focal boost to IPLs provides a feasible, safe, and biochemically effective RT approach for localized PC.

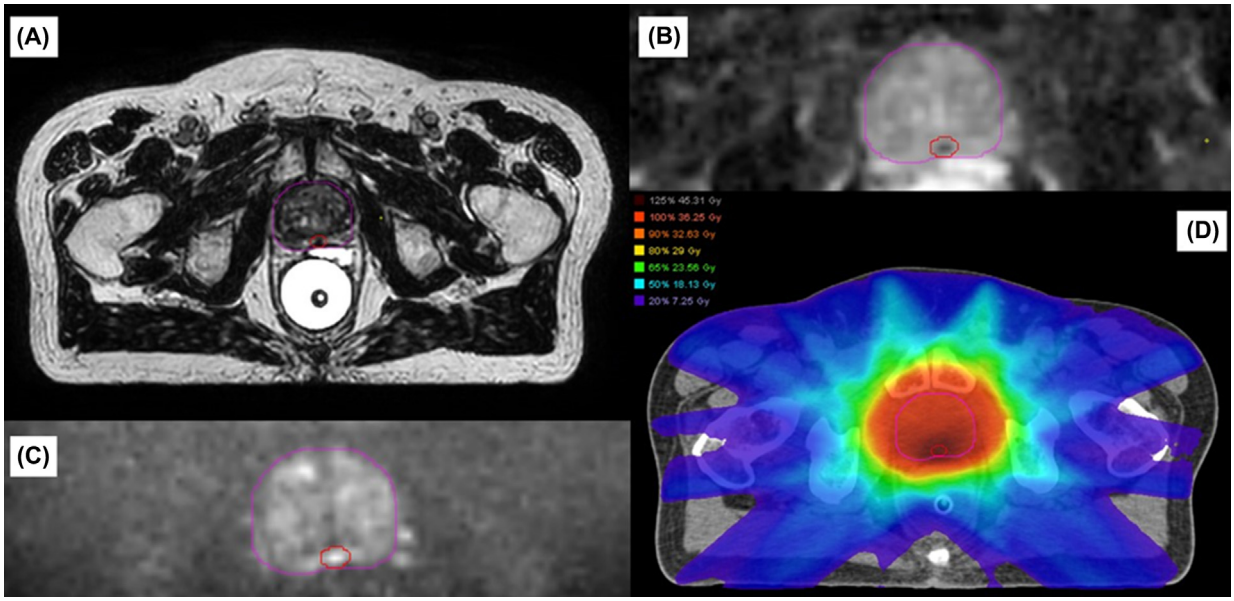

Fig. 1 – Example of a focal boost plan: (A) T2-weighted image on a Elekta Unity magnetic resonance Linac system; (B) apparent diffusion coefficient image; (C) diffusion-weighted imaging with a *b* value of 1400 s/mm^2; and (D) dose distribution on the reference computed tomography. Dose prescriptions to the prostate gland (solid magenta line) and dominant intraprostatic lesion (solid red line) were 36.25 Gy and 42 Gy, respectively.

2. Evidence acquisition

2.1. Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [18] was followed. Comprehensive literature searches of PubMed/MEDLINE, Embase, and Web of Science were conducted independently by three authors (J.Y., O.L.W., and D.M.C.P.) in February 2022, which included all types of publications from 2000 to 2021. Databases were searched using the search string "((prostate cancer) OR (prostate)) AND ((radiotherapy) OR (radiation therapy) OR (escalation) OR (focal boost) OR (dose painting) NOT (brachytherapy)) AND ((intraprostatic lesion) OR (intraprostatic nodule) OR (intra-prostatic) OR (dominant))".

2.2. Study selection

The Population, Intervention, Comparator, Outcome, and Study Design (PICOS) method was used to define the literature inclusion criteria (Supplementary Table 1). The exclusion criteria were: (1) retrospective data and analysis; (2) studies involving nonhuman subjects or patients with metastatic PC; (3) patients undergoing irradiation other than EBRT; (4) IPLs identified or delineated using modalities other than MRI; (5) pure planning studies or studies not reporting any clinical outcome; (6) publications not in English; and (7) books, conference abstracts, case reports, and reviews. If multiple publications were generated with substantial patient overlap, only the latest publication with the largest patient size was included. References in relevant reviews were examined to identify extra studies for potential inclusion.

2.3. Data extraction

Data extraction was conducted and reviewed independently by three authors (J.Y., D.M.C.P., and O.L.W.). Disagreement was resolved via discussion. Oxford Centre for Evidence-Based Medicine 2011 levels of evidence (https://www.cebm.ox.ac.uk/files/levels-of-evidence/cebm-levels-of-evidence-2-1.pdf) were assigned to each study by two authors (J.Y. and D.M.C.P.). Comprehensive data were extracted and cross-checked, including the study and patient characteristics, treatment planning and delivery, and clinical outcomes. In cases for which information or values to be extracted were not explicitly reported, but could be calculated or indicated from other reported data, we aimed to provide such information to minimize missing data.

2.4. Statistical analysis

Statistical analyses were performed using R Studio version 1.1.383 (R Foundation for Statistical Computing, Vienna, Austria). Individual study effect sizes were modeled as percentages: the denominator was the total patient number, and the numerator was the number of patients having the particular measure of interest, multiplied by 100. The R package *metafor* version 3.4 (R Foundation for Statistical Computing) was used to conduct meta-analyses. Forest plots were generated to determine pooled summary estimates of acute and late gastrointestinal (GI) and genitourinary (GU) toxicities and biochemical outcomes, along with the corresponding 95% confidence interval (CI) and associated 95% prediction interval (PI) based on weighted random-effects models. Heterogeneity was quantified using I^2 statistics. High heterogeneity was indicated by a 95% CI for I^2 of >50%. The p value calculated via a t test based on the weighted linear regression of the effect estimates on their standard errors was used to quantify the funnel plot asymmetry, with $p < 0.05$ indicating publication bias.

3. Evidence synthesis

The literature search yielded 693 publication records for screening after removal of duplicates. After screening, 38 full-text articles were assessed for eligibility. Of these, 21 were excluded and 17 prospective studies were ultimately included [19–35]. Figure 2 shows the PRISMA flow diagram. The complete list of studies that were excluded is provided in the Supplementary material.

3.1. Study characteristics

In the 17 studies included in the review (Table 1), a total of 1290 patients underwent MRI-guided EBRT focal boost to IPLs. There were 14 single-center studies and three multicenter studies, including one randomized phase 3 trial [32]. Eight studies included patients with low-risk (LR), intermediate-risk (IR), and high-risk (HR) disease; two studies only included HR cases, and a further two studies included no HR cases. The remaining five studies included both IR and HR cases, but no patients with LR disease. The majority of patients (847/1290; 65.7%) received androgen deprivation therapy (ADT) concomitant with EBRT (range across studies 5–100%). Sixteen studies presented results for clinician-reported toxicity (acute toxicity only: $n = 3$; late toxicity only: $n = 2$; both: $n = 11$) [34]. Nine studies presented results for patient-reported quality of life (QoL). Fourteen studies reported biochemical disease and/or oncological outcomes.

3.2. Patient characteristics

Supplementary Table 2 summarizes the patient characteristics. Most studies reported baseline prostate-specific antigen (PSA), clinical T stage, and Gleason score or International Society of Urological Pathology grade for risk stratification. All studies explicitly reported on the risk stratification distribution, but with different criteria. Overall, the numbers of patients with LR, IR, and HR disease were 63 (4.9%), 532 (41.2%), and 695 (53.9%), respectively.

3.3. MRI for IPL identification and delineation

All IPLs were initially identified by 1.5-T or 3-T diagnostic mpMRI, following the Prostate Imaging-Reporting and Data System guideline [12,13], with or without an endorectal coil. Diagnostic MRI was usually fused with planning computed tomography (CT), but the images were occasionally displayed side by side to aid IPL contouring without image registration [26]. Different MRI images might have different

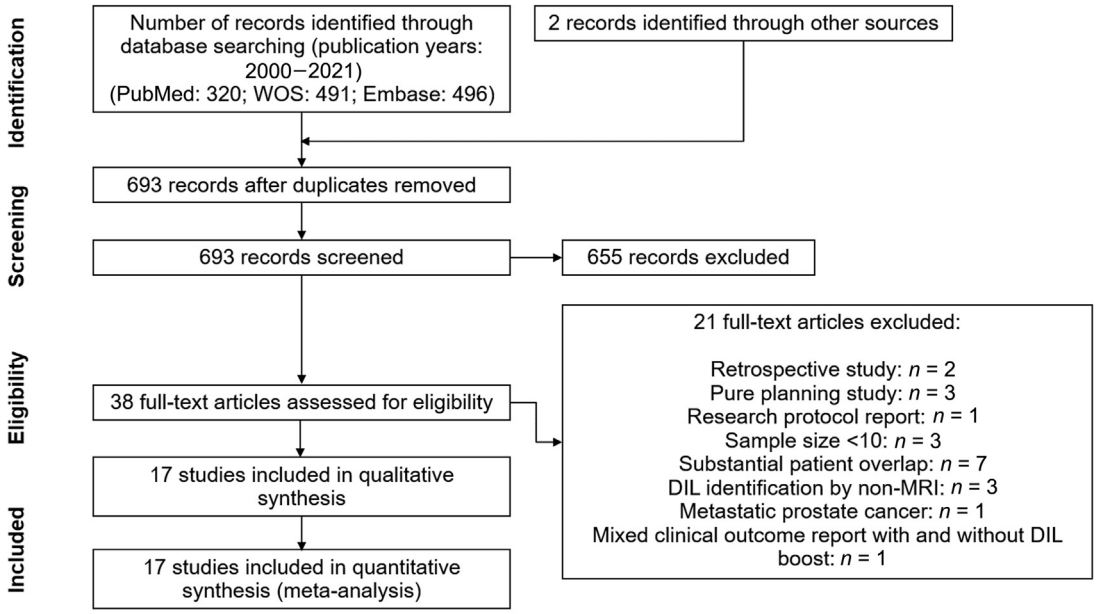

Fig. 2 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.WOS = Web of Science; MRI = magnetic resonance imaging; DIL = dominant intraprostatic lesion.

roles in IPL delineation, as demonstrated by the tumor contouring in the FLAME trial [32,36], but were not explicitly described in all studies. A second planning MRI in the treatment position was also acquired in some studies, mainly for better CT-MRI co-registration [23,24,28,33,35]. Only one study used both mpMRI and prostate-specific membrane antigen (PSMA) positron emission tomography (PET) for IPL identification and delineation [34]. It is unclear whether all MRI-identified IPLs were delineated and underwent a dose boost. Criteria for IPL eligibility for a dose boost were not clarified in many studies.

3.4. *Treatment planning and delivery*

Supplementary Table 3 summarizes the information on treatment planning and delivery. The prostate/IPL dose prescription, margin setting, fractionation, dose metric objectives, and constraints were highly heterogeneous. The IPLs and whole prostate (plus seminal vesicles if involved) were normally defined as the gross tumor volume (GTV) and clinical target volume (CTV), respectively. The GTV-CTV margin ranged from 0 to 6 mm, mostly with isotropic extension. The CTV-planning target volume (PTV) margin ranged from 3 to 10 mm. A smaller posterior CTV-PTV margin was usually set. Except for two studies in which the IPL boosts were conducted before [28] and after [19] standard fractionated treatment, IPL boosts were delivered simultaneously. Not all studies reported the assumed α/β ratio for dose planning, for which a value of 1.5 or 3 was most frequently used. Prescription doses to PTVprostate and PTV_{IPL} were as follows: 64–78 Gy (equivalent dose 2 [EQD2] 64–81.8 Gy) and 74–95 Gy (EQD2 80–123 Gy) in nine studies with conventionally fractionated EBRT (total fractions $\geq$32); 60 Gy (EQD2 72 Gy) and 67–68 Gy (EQD2 85.1–87 Gy) in the two studies with moderate hypofractionated EBRT (20 fractions); and 35–47.5 Gy (EQD2 85–118.7 Gy) and 37.5–55 Gy (EQD2 96.4–164.3 Gy) in the seven studies with ultra-hypofractionated EBRT (five fractions). One study conducted both conventional and moderate hypofractionation in two arms for comparison [26]. The number of concerning OARs, their contouring guidelines, and dose constraints varied among the studies. The rectum and bladder were always included and preserved from overdose in all studies. Urethra-sparing was conducted in 13 studies. Bladder and rectum control were mostly conducted, with variable protocols among studies. A full bladder and an empty rectum were most frequently used. Rectal balloons and/or hydrogel rectal spacers were optionally used. Despite the various treatment modalities and techniques, most studies relied on implanted fiducial markers for prostate alignment and/or intrafractional motion tracking. Eleven studies reported achievement of treatment plan quality. Dose objectives and constraints were met in most studies.

3.5. *Clinical outcomes*

Supplementary Table 4 summarizes the clinical outcomes reported in the studies.

3.5.1. *GI and GU toxicity*

The Common Terminology Criteria for Adverse Events (CTCAE) and Radiation Therapy Oncology Group (RTOG) tools were most commonly used for toxicity evaluation.

Table 1 – Characteristics of the studies included in the review

Study	Centers and phase	LE	Location	Treatment period	Patients (*n*)	mFU, mo (range)	Risk group, *n* (%)			ADT (%)	Outcomes measured			
							Low	Intermediate	High		Toxicity		QoL	B/OO
											Acute	Late		
Miralbell 2010 [19]	SC	2	Barcelona, Spain	Jun 2001–Apr 2004	50	63 (18-88)	5 (10)	12 (24)	33 (66)	66	Yes	Yes	No	Yes
Schild 2014 [20]	SC	2	Arizona, USA	Feb 2009–Feb 2013	78	36 (4-57)	18 (23)	43 (55)	17 (22)	41	Yes	Yes	No	Yes
Garibaldi 2016 [21]	SC; phase 2	2	Torino, Italy	Mar 2012–Dec 2014	15	16 (2-39)	0 (0)	14 (93.3)	1 (6.7)	100	Yes	Yes	No	Yes
Sundahl 2016 [22]	SC	2	Ghent, Belgium	Jan 2002–Nov 2014	IPL: 225 nIPL: 185	IPL: 60 (1–132) nIPL: 72 (6–144)	IPL: 5 (2) nIPL: 18 (10)	IPL: 97 (43) nIPL: 93 (50)	IPL: 123 (55) nIPL: 74 (40)	98 (IPL)	Yes	Yes	No	Yes
Onjukka 2017 [23]	SC; phase 2 NCT02125175	2	Bebington, UK	Oct 2002–Aug 2006	28	37 (32–45)	0 (0)	0 (0)	28 (100)	100	Yes	Yes	Yes	Yes
Herrera 2019 [24]	SC; phase 1a/b NCT02254746	2	Lausanne, Switzerland	Oct 2014–Apr 2017	20	24 (6–39)	0 (0)	7 (35)	13 (65)	5	Yes	Yes	Yes	Yes
McDonald 2019 [25]	SC NCT01856855	2	Alabama, USA	Sep 2013–Jan 2017	26	Up to 90 d	6 (23)	20 (77)	0 (0)	30.8	Yes	No	No	No
Murray 2020 [26]	SC; phase 2 ISRCTN04483921	2	London, UK	Jul 2011–Jan 2015	55 (cohort A)	74.5	0 (0)	40 (73)	15 (27)	100	Yes	Yes	Yes	Yes
					50 (cohort B)	52	0 (0)	30 (60)	20 (40)	100	Yes	Yes	Yes	Yes
Alayed 2020 [27]	SC; phase 2 NCT01953055, NCT02911636	2	Toronto, Canada	2013–2017	IPL: 30 nIPL: 30	5STAR, IPL: 25 SATURN, nIPL: 60	0 (0)	11 (36.7)	19 (63.3)	100	Yes	Yes	Yes	No
Pollack 2020 [28]	SC; phase 1 NCT01411319	2	Florida, USA	Not reported	25	66 (20.8–71.1)	2 (8.7)	17 (73.9)	4 (17.4)	56	Yes	Yes	No	Yes
Draulans 2020 [29]	4-center; phase 2 NCT02853110	2	Netherlands; Belgium	Apr 2016–Dec 2018	100	6	0 (0)	25 (25)	75 (75)	62	Yes	No	No	No
Marvaso 2020 [30]	SC; phase 2 NCT01913717	2	Milan, Italy	Oct 2014–Jan 2018	65	Up to 2 yr	13 (20)	52 (80)	0 (0)	8	Yes	No	Yes	Yes
Buwenge 2020 [31]	SC; phase 1/2	2	Italy	Not reported	44	120 (25–150)	6 (13.6)	18 (40.9)	20 (45.5)	100	No	Yes	No	Yes
Kerkmeijer 2021 [32]	4-center; phase 3 NCT01168479	1	Netherlands; Belgium	Nov 2009–Feb 2015	FBA: 284 SA: 287	72 (58–86) [a]	2 (1)	43 (15)	239 (84)	60	No	Yes	Yes	Yes
Zapatero 2021 [33]	SC; phase 2 NCT03030625	2	Madrid, Spain	Mar 2017–Jan 2020	30	30 (25.5–40.72) [a]	4 (13.3)	15 (50)	11 (36.67)	50	Yes	Yes	Yes	Yes
Eade 2021 [34]	2-center	2	Sydney, Australia	Jul 2015–Jun 2019	112	2.3 yr	2 (1.8)	88 (78.6)	22 (19.6)	5.4	No	No	Yes	Yes
Hannan 2021 [35]	SC; phase 1 NCT02353819	2	Texas, USA	Nov 2015–Oct 2019	55	18 (3–48)	0 (0)	0 (0)	55 (100)	100	Yes	Yes	Yes	Yes

ADT = androgen deprivation therapy; mFU = median follow-up; QoL = quality of life; B/OO = biochemical or oncological outcome; IPL = intraprostatic lesion; nIPL = no IPL; LE = level of evidence (Oxford Centre for Evidence-Based Medicine); FBA = focal boost arm; SA = standard arm; SC = single center.

[a] Interquartile range.

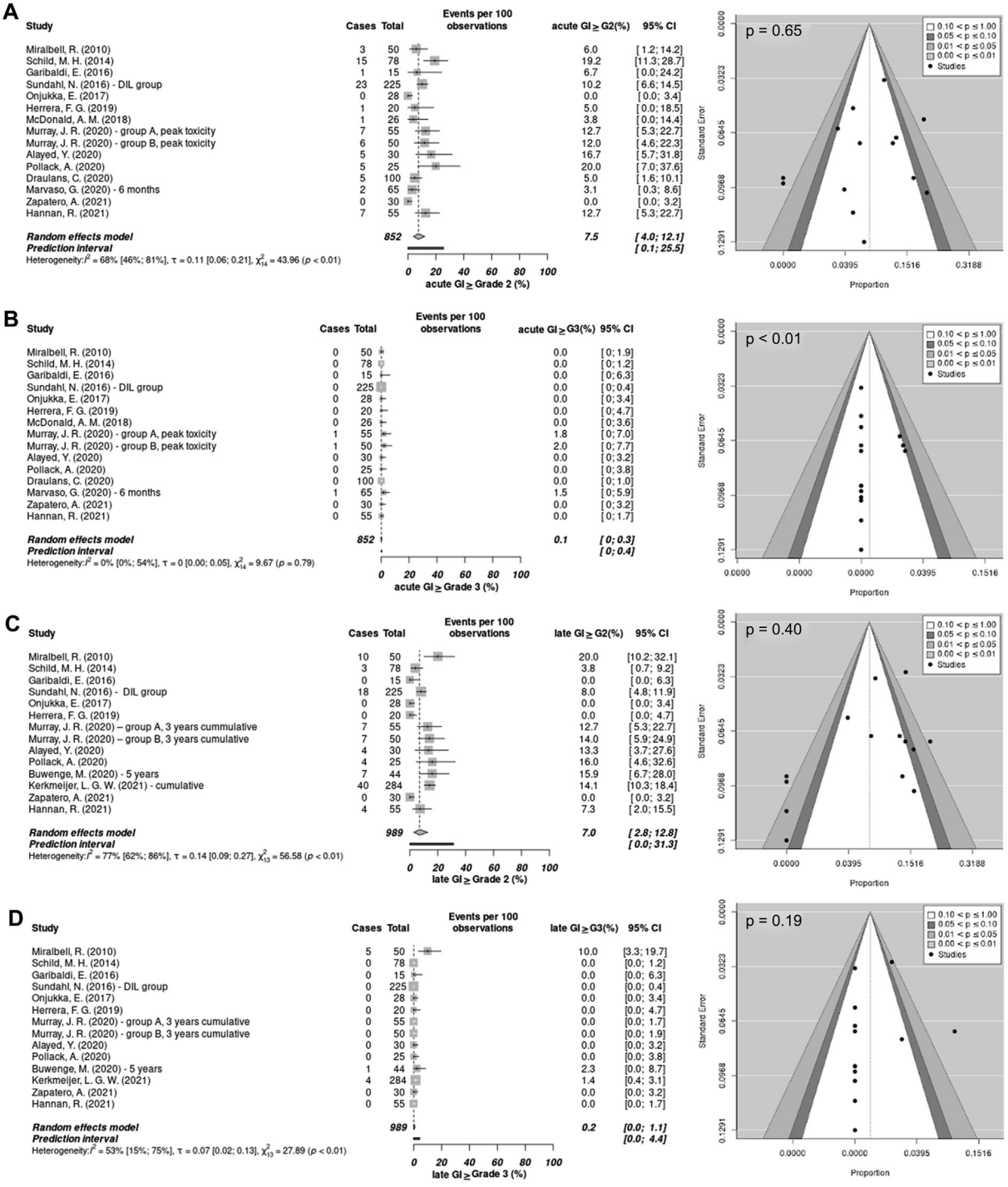

Fig. 3 – Forest plots and funnel plots for (A) acute grade ≥2, (B) acute grade ≥3, (C) late grade ≥2, and (D) late grade ≥3 GI toxicities. CI = confidence interval; GI = gastrointestinal.

The rates of grade 1 (G1), G2 and ≥G3 acute GI toxicity were 6.6–51%, 0–20%, and 0–<2%, respectively. Estimated rates of acute GI toxicity based on the random-effects model were 7.5% (95% CI 4.0–12.1%; 95% PI 0.1–25.5%) for ≥G2 and 0.1% (95% CI 0–0.4%; 95% PI 0–0.4%) for ≥G3. G1, G2, and ≥G3 late GI toxicity rates reported were 5.0–44%, 0–16.0%, and 0–10.0%, respectively. Pooled late GI toxicity rates were 7.0% (95% CI 2.8–12.8%; 95% PI 0%–31.3%) for ≥G2 and 0.2% (95% CI 0–1.1%; 95% PI 0–4.4%) for ≥G3. Figure 3 shows forest plots and funnel plots for ≥G2 and ≥G3 GI toxicities. Except for acute ≥G3 GI toxicity, rates of other toxicities were highly heterogeneous (I^2 > 50%). Significant publication bias was only found for acute ≥G3 GI toxicity (p < 0.01), probably because of its extremely low incidence.

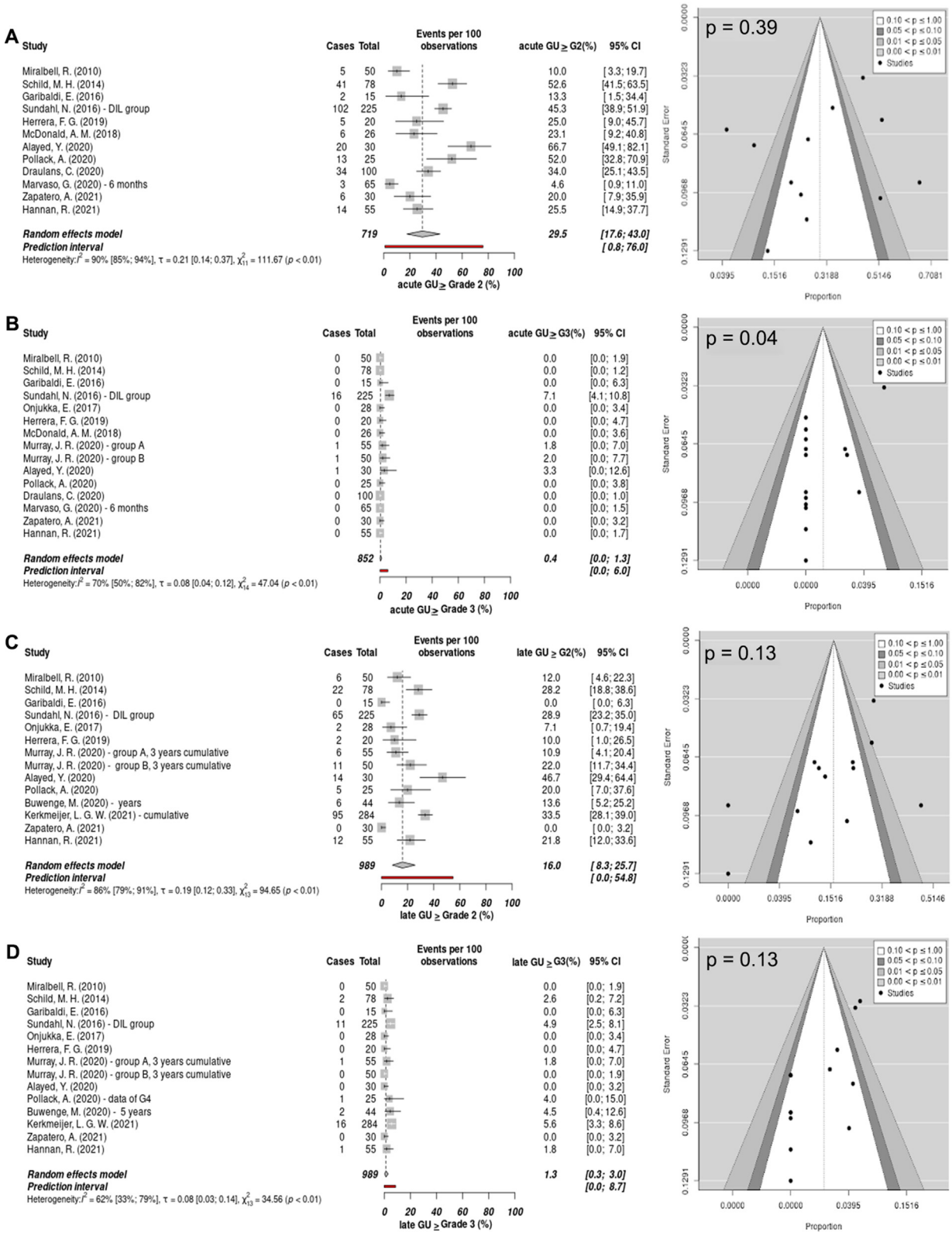

Fig. 4 – Forest plots and funnel plots for (A) acute grade ≥2, (B) acute grade ≥3, (C) late grade ≥2, and (D) late grade ≥3 GU toxicities. CI = confidence interval; GU = genitourinary.

The acute GU toxicity rates reported were 19.2–45% for G1, 4.69–63.3% for G2, and 0–7% for ≥G3, all of which are higher than the corresponding acute GI toxicity rates. Figure 4 shows forest plots and funnel plots for ≥G2 and ≥G3 GU toxicities. The GU toxicity rates reported were all heterogeneous (I^2 > 50%). Pooled rates for acute GU toxicity

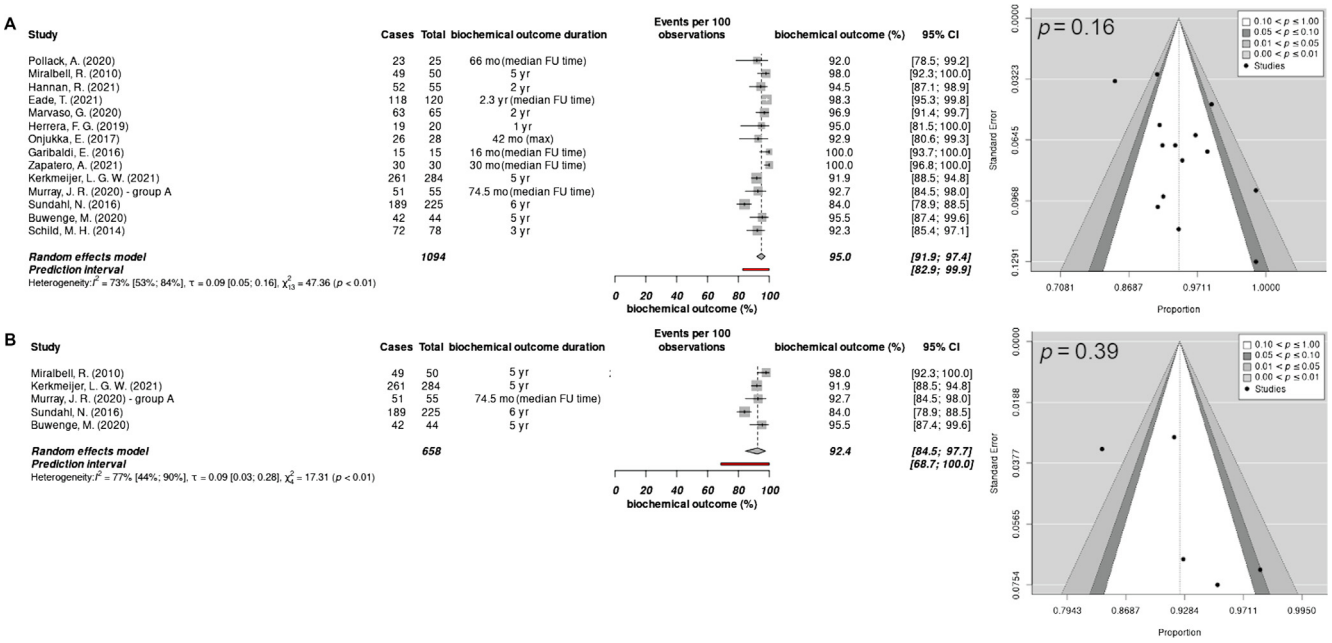

Fig. 5 – Forest plot and funnel plot of reported biochemical outcomes with (A) >1 yr and (B) >5 yr of follow-up.CI = confidence interval; FU = follow-up.

based on the random-effects model were 29.5% (95% CI 17.6–43.0%; 95% PI 0.8–76%) for ≥G2 and 0.4% (95% CI 0.0–1.3%; 95% PI 0.0–6.0%) for ≥G3. For late GU toxicity, the G1, G2 and ≥G3 rates reported were 9.1–60%, 0–46.67%, and 0–5.6%, respectively. The random-effects model estimated late GU toxicity rates of 16.0% (95% CI 8.3–25.7%; 95% PI 0–54.8%) for ≥G2 and 1.3% (95% CI 0.3–3.0%; 95% PI 0–8.7%) for ≥G3. There was significant publication bias for acute ≥G3 GU toxicity (p = 0.04).

3.5.2. *Patient-reported QoL*

Although nine studies reported QoL results, meta-analysis could not be conducted because the qualitative or semi-quantitative results were derived from different assessment tools. In the FLAME trial, no significant QoL differences were observed between the IPL boosting and control arms [32]. Onjukka et al [23] observed similar Expanded Prostate Cancer Index Composite (EPIC) bowel domain–specific summary and subscale scores between patients with PC and control subjects without PC. Reductions in EPIC urinary domains were also similar among different treatment cohorts. Herrera et al [24] showed minimal impacts in GU, GI and sexual domains of IPL dose escalation to 50 Gy in a five-fraction scheme. QoL results reported by Murray et al [26] showed no substantial changes with IPL boosting treatment in two cohorts. The EPIC results (cohort B only) showed no substantial change in some urinary symptoms during follow-up, and recovery of bowel symptoms to baseline by month 24. The sexual domain scores were markedly deteriorate while on ADT and continued to decline after completion of RT and ADT [26]. Alayed et al [27] reported nonsignificant urinary, bowel, and sexual QoL differences with and without IPL boosting. Marvaso et al [30] found that patients had nonsignificant QoL changes during follow-up. Zapatero et al [33] reported that urinary, bowel, and sexual bother EPIC scores nonsignificantly increased in the first 3 mo after treatment, and then returned to normal. In the study by Eade et al [34], 89% of patients reported "no regret" regarding their treatment, and only 8% and 6% of patients reported "quite a lot" or "very much" for urinary and bowel bother, respectively, suggesting overall satisfaction with treatment. In the multilevel dose escalation trial, small decreases in EPIC scores in GI and GU were observed at 1.5 mo, and lower EPIC scores were seen in GU at 12 mo and in GI at 18 mo relative to baseline and month 3 [35].

3.5.3. *Biochemical outcomes*

bDFS in 14 studies ranged from 84.0% to 100% up to median follow-up of 74.5 mo. Most studies defined biochemical failure using the Phoenix definition (PSA nadir + 2 ng/ml). In the FLAME trial [32], 5-yr bDFS in the focal boost arm (n = 264) was significantly higher (92% vs 85%; hazard ratio 0.45, 95% CI 0.28–0.71; p<0.001) than in the standard arm without focal boost (n = 271).

The synthesized bDFS for all studies was 95.0% (95% CI 91.9–97.4%; 95% PI 92.9–99.9%), without publication bias (p = 0.12) but with high heterogeneity (I^2 = 73%; Fig. 5). For the five studies with follow-up >5 yr, the estimated bDFS was 92.4% (95% CI 84.5–97.7%; 95% PI 68.7–100%).

3.5.4. *Other oncological outcomes*

Overall survival (OS), which was explicitly reported in several studies, might be expected to reach 100% over short follow-up. Schild et al [20] reported 3-yr OS of 95% among 78 patients. The 2-yr OS in the phase 2 "Give Me Five" trial was 98% among 65 patients with LR or IR disease [30].

Buwenge et al [31] reported 5-yr and 10-yr OS of 95.5% and 87.8%, respectively, among 44 patients. In a study of 55 HR cases, Hannan et al [35] reported 2-yr actuarial OS of 98.2% with multilevel dose escalation.

Miralbell et al [19] reported 100% 5-yr disease-specific survival (DSS) among 50 patients. In FLAME [32], the focal boost arm showed significantly better DFS (log-rank $p < 0.001$) up to 7 yr. PC-specific survival did not significantly differ (log-rank $p = 0.49$). Hannan et al [35] reported 2-yr actuarial DSS of 100% among 55 HR cases.

Regarding local control rates, Schild et al [20] reported 98% at 3 yr among 78 PC patients, while Buwenge et al [31] reported 97.7% at 5 yr and 94.9% at 10 yr among 44 patients. In cohort A in the study by Murray et al [26], one of 55 patients (~1.8%) had radiological evidence of local disease recurrence. Zapatero et al [33] reported 100% local control using mpMRI; 25 patients had complete responses after treatment at 6 mo. In the remaining five patients, complete IPL disappearance on both T2 and DWI was observed at 9 mo after treatment. Regarding metastasis control, Schild et al [20] reported a distant metastasis control rate of 95% at 3 yr among 78 PC patients. Onjukka et al [23] reported that one of 28 patients (~3.6%) had pelvic nodal relapse at 36 mo. In the study by Murray et al [26], two of 55 patients (~3.6%) in cohort A had radiological evidence of pelvic nodal metastasis ($n = 1$) or distant rib metastasis ($n = 1$). Buwenge et al [31] reported metastasis-free survival (MFS) rates of 100% at 5 yr and 97.6% at 10 yr ($n = 44$). In FLAME [32], there was nonsignificant difference (log-rank $p = 0.26$) in distant MFS up to 7 yr between the two arms. A further analysis showed that focal boosting decreased local failure (hazard ratio 0.33; 95%CI 0.14–0.78) and regional + distant MFS (hazard ratio 0.58, 95% CI 0.35–0.93) [37]. Eade et al [34] reported that two of 112 patients (~1.8%) had bone metastases on PSMA PET during median follow-up of 2.3 yr.

3.6. Discussion

All studies demonstrated the feasibility, safety, patient tolerance, and applicability of MRI-guided EBRT focal boost to IPLs in localized PC. Despite the large heterogeneity, the findings highlight encouraging clinical outcomes of low toxicity, satisfactory QoL, and high bDFS with this treatment. In particular, two studies reported comparative outcomes between whole-prostate irradiation with and without IPL focal boost. Sundahl et al [22] reported that the actuarial risk of developing toxicity and the incidence of symptoms were not increased by IPL boost (median follow-up 72 mo). Level 1 evidence was provided by the FLAME trial, which reported a significant improvement in 5-yr bDFS with MRI-guided IPL focal boost [32].

Our pooled results for ≥G3 GI toxicity rates of 0.1% (95% CI 0–0.4%; 95% PI 0–0.4%) for acute cases and 0.2% (95% CI 0–1.1%; 95% PI 0–4.4%) for late cases are lower than those in the previous systematic review (5% for acute cases, two studies; 2.5% for late cases, five studies), which included only two EBRT studies [17]. The ≥G3 GU toxicity rates were also lower in this study, at 0.4% (95% CI 0.0–1.3%; 95% PI 0.0–6.0%) for acute cases and 1.3% (95% CI 0.3–3.0%; 95% PI 0–8.7%) for late cases, compared with 4.4% (acute, six studies) and 3.1% (late, five studies) previously [17].

Regarding patient-reported QoL, most patients experienced good tolerance, in line with the clinician-reported toxicity results. However, the heterogeneity in QoL tools and qualitative or semi-quantitative QoL reporting hampered the pooled meta-analysis.

The estimated median bDFS was 95.0% (range 84.0–100%; 95% CI 91.9–97.4%; 95% PI 92.9–99.9%), without significant publication bias ($p = 0.12$). This is also higher than the previously reported rate of 85% (range 78.8–100%; 95% CI 77.1–82.7%) [17].

Several factors may explain the lower grade ≥3 toxicity rates and better bDFS in our review. First, we included more recent studies. Technical advances in MRI, treatment planning, and IGRT may synergistically improve the treatment precision of MRI-guided IPL focal boost by depositing the high-boost dose on better-defined and -guided targets without exceeding OAR constraints. Second, differences in the implementation of IPL focal boost by EBRT and brachytherapy (majority in [17]) may partly explain the differences in results. The higher proportion of patients receiving ADT (65.7%) in our cohort might have contributed to better bDFS in comparison with the previous meta-analysis, in which only 27.8% of patients received ADT [17]. Notably, the bDFS observed was higher than that in the previous systematic review, despite the higher proportion of HR cases included in our analysis.

At present, studies frequently use diagnostic mpMRI for IPL identification and delineation. This procedure is far from optimized or standardized. MRI with a 3-T scanner is considered preferable to 1.5-T MRI because of its higher signal-to-noise ratio (SNR) and better image quality, but suffers from greater distortion. Diagnostic T2W-MRI is typically obtained using two-dimensional sequences with relatively thick slices. The role of DCE-MRI is uncertain. DWI is associated with low resolution, poor SNR, and large distortion. Meanwhile, diagnostic mpMRI is usually acquired before ADT initiation. Accurate CT-MRI co-registration is challenging because of variations in patient positioning, rectal/bladder filling, and ADT-induced prostate/IPL downsizing effects. These may be improved by dedicated MRI simulators and planning MRI based on three-dimensional sequences, preferably acquired with a minimal interval to the planning CT [38–40]. RT planning based solely on MRI-generated synthetic CT, which eliminates CT-MRI co-registration uncertainties, is also increasing in popularity [41,42].

This meta-analysis involved many more IR and HR cases than LR cases. The role of IPL boost in LR disease remains largely unknown. There are few studies and thus scarce evidence to support or reject IPL focal boost in patients with LR cancer. It is also unclear which types of IPL should be eligible for dose escalation. Large variability in GTV was observed among the studies. There was also variability in the use of ADT combined with IPL boost, which affected IPL delineation on MRI and clinical outcomes. Results are awaited from an ongoing study (NCT05169970) evaluating the potential benefit of IPL boost without ADT in disease with high genomic risk. Given the recent evidence showing

better biochemical outcomes with pelvic RT in HR disease [43], the role of simultaneous ultra-hypofractionated pelvic RT and IPL boost is currently being addressed in the 5STAR-PC (NCT04245670) and PIVOTALboost (ISRCTN80146950) studies [44].

Substantial differences in RT planning and treatment delivery were observed among the studies included in the review. Large variability in margin setting to the IPL boundary (GTV-CTV margin) was applied (range 0–6 mm). At present, IPL contouring guidelines remain unavailable. Despite the variability in dose prescription and fractionation, the safety of IPL boost has been demonstrated in all dose escalation schemes, largely relieving concerns about potential related toxicities. Different OARs were included in plans, with variations in dose constraints, potentially affecting the toxicity and QoL outcomes reported. The interval between neoadjuvant ADT initiation and RT planning and delivery was seldom reported. Regarding treatment delivery, different treatment modalities and irradiation techniques were used. If online imaging guidance was implemented, fiducial markers implanted before treatment were necessary because current online imaging tools, mostly X-ray-based, poorly visualize the prostate and IPL.

This review did not include any studies that implemented IPL delineation and irradiation using the recently introduced MRI linear accelerator (MR-LINAC) technology [45]. MRI-guided RT using MR-LINAC promises to further improve IPL boost precision and thus clinical outcomes via its unique capability for online plan adaption and real-time motion management without implanted fiducial markers [46–48].

Our review has some limitations. First, some eligible patients may have been excluded because we only included English-language publications and excluded studies that reported mixed outcome results with and without IPL boost [49,50]. Second, all individual patient data were not accessible, so patient-specific covariates could not be adjusted for, although the inclusion of only prospective studies partly mitigated this issue. Third, the studies included were heterogeneous, although we made efforts to mitigate many confounding factors. There was considerable between-study variability for the patient characteristics, MRI utilization, treatment planning and delivery, and outcome metrics, all leading to the large I^2 values. They also partly account for the bias observed. Fourth, the small study sample size and inaccessibility to individual data also hindered a meaningful meta-regression. Finally, the evidence level was relatively low, with only one level-1 randomized phase 3 trial [32]. Longer follow-up data were not available to demonstrate a definitive benefit in terms of OS or other oncological outcomes with IPL boost.

4. Conclusions

We reviewed current utilization and performance of MRI-guided focal boost to IPLs using EBRT in localized PC. All the studies included demonstrated the feasibility and applicability of this treatment, along with good safety and patient tolerance. The meta-analysis showed low GI and GU toxicities and excellent biochemical outcomes. However, considering the limited and heterogeneous data, some of these findings are not definitive. More prospective trials focusing on hypofractionation or ultra-hypofractionation with this approach are warranted.

Author contributions: Darren M.C. Poon had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Poon, Yuan, Wong, Yang.
Drafting of the manuscript: Poon, Yuan.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2022.10.001.

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