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Review Article

Comparison of chronic gastrointestinal and genitourinary toxicities between brachytherapy and external beam radiotherapy for patients with prostate cancer: A systematic review and meta-analysis

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Abstract.
BACKGROUND: ^{125}I BT is an effective radiotherapy for prostate cancer. However, comparison data of GI and GU toxicities between BT, BT + EBRT, and EBRT-alone patient groups is limited.
OBJECTIVE: To define the GI and GU toxicities in prostate cancer to prevent adverse events after treatment.
METHODS: We searched published studies in PubMed, Cochrane, and Embase databases up to December 31, 2022. The endpoints were the RRs of GI and GU toxicities. Pooled data were assessed using a random-effects model.
RESULTS: Fifteen eligible studies were included into this analysis. LDR-BT had significantly lower RRs than LDR-BT + EBRT for acute GI (2.13; 95% CI, 1.22–3.69; $P = 0.007$) and late GI toxicities (3.96; 95% CI, 1.23–12.70; $P = 0.02$). Moreover, EBRT had significantly higher RRs than LDR-BT for acute GU (2.32; 95% CI, 1.29–4.15; $P = 0.005$) and late GU toxicities (2.38; 95% CI, 1.27–4.44; $P = 0.007$). HDR-BT had significantly higher RRs for acute GU toxicities than LDR-BT alone (0.30; 95% CI, 0.23–0.40; $P < 0.00001$).
CONCLUSION: The results implied that BT with and without EBRT can result in both GI and GU toxicities in patients with prostate cancer, with LDR-BT leading to a poorer urinary function than EBRT.

Keywords: Prostate cancer, gastrointestinal, genitourinary, brachytherapy, external beam radiotherapy, meta-analysis

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1. Introduction

Prostate cancer is malignant tumor worldwide that threatens the health of older men [1]. Currently, transperineal interstitial permanent (Iodine) ^{125}I-brachytherapy (BT) with or without EBRT is an effective and widely used treatment for localized prostate cancer [2]; this is because BT provides a good conformal dose distribution to the prostate [3]. Moreover, the oncologic outcomes of permanent BT are similar to those of surgical treatment and EBRT, and BT has low toxicity rates [4].

BT is a recommended monotherapy for low-malignant prostate cancer and boost for intermediate- and high-risk prostate cancer [5–8]. The incidence of gastrointestinal (GI) and genitourinary (GU) toxic adverse events (AEs) varies with the choice of treatment. Given that the outcomes of BT, RP, and EBRT are similar, the prognosis accuracy, selection of a treatment regimen, and risks of GI and GU toxicities during and after radiotherapy (RT) are important. GI and GU toxicities from RT options should be considered because of their impact on patients' health [9,10]. The concern with BT is its toxicity to nearby organs and tissues, particularly with respect to GI and GU health [11].

An optimal therapeutic outcome would include maximal survival benefits with low GI and GU toxicities. Several clinical studies have indicated that BT, EBRT, and their combined therapy may be associated with a high prevalence of different GI and GU toxicities. However, there is no meta-analysis of recent clinical studies. Therefore, we assessed the risks of GI and GU toxicities from BT, EBRT, and combined-treatment use in men with prostate cancer.

2. Materials and methods

2.1. Literature search

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was registered at PROSPERO (Number: CRD42021249602) [12].

The literature was searched in Cochrane Library, PubMed and Embase databases up to December 31, 2022. The following Mesh keywords were used during the search: "prostatic neoplasms," "prostatic intraepithelial neoplasia," "brachytherapy," "Iodine-125," "I-125," and "125I."

2.2. Inclusion and exclusion criteria

The inclusion criteria for clinical studies were as follows: only cohort studies in adult men with localized prostate cancer; no lymph node involvement; no distant metastases; comparisons between ^{125}I-BT, EBRT, and ^{125}I-BT combined with EBRT; reported AEs involving acute and late post-treatment GI and GU toxic complications (CTCAE or RTOG) [13–15] during follow-up visits; and types of EBRT radiation treatment including intensity-modulated radiation treatment, 2-dimensional conventional radiation treatment and 3-dimensional conformal radiation treatment. Studies with incomplete data were excluded.

2.3. Data extraction

Studies were extracted by two reviewers independently to identify eligible studies. A third reviewer arbitrated any disagreements. These data included year of publication, first author, country of origin, study design, enrollment period, type of the patients, sample sizes, type of interventions, follow-up time, and details of toxic outcomes. The endpoints of GI and GU toxic complications were defined as AEs based on the CTCAE or RTOG. Only events greater than grade 2 were considered.

2.4. Quality assessment

The Newcastle-Ottawa scale (NOS) to evaluate the quality of the clinic studies. Quality assessment included measurement of exposure factors, among-group similarity, and patient selection. Any disagreement was resolved by consensus. Studies with NOS scores $\geqslant 6$ were considered as high-quality and studies with NOS scores < 6 were considered as low-quality.

2.5. Statistical analysis

A pooled estimate of the differences in risk for the single studies was calculated using a random-effect model base on the Mantel-Haenszel method; the results of studies are illustrated using forest plots. Dichotomous parameters were expressed as risk ratios (RRs). All results of studies were presented with a 95% confidence interval (95% CI). Homogeneity within the data of each study was assessed using a chi-square test, setting the degrees of freedom to the number of analyzed studies minus one. Heterogeneity was observed with the Cochran Q test and I^2 statistics, which quantifies inconsistency across studies to assess the impact of meta-analysis heterogeneity. An I^2 statistic above 50% indicates significant heterogeneity. Heterogeneity was assessed using sensitivity analysis. Analyses of all gathered data were conducted with Review Manager Version 5.3 (Cochrane, London, United Kingdom).

3. Results

3.1. Study selection

We identified 16 213 potentially relevant studies. After removing 4407 duplicate studies, the title and abstract of the remaining 11 806 studies were assessed. Of these, 11 745 studies removed without inclusion criteria. Finally, 15 studies were included in the meta-analysis (Fig. 1): four prospective cohort studies and 11 retrospective cohort studies [16–30].

3.2. Study characteristics

Of the 12 773 patients in the included studies, 9405 were treated with LDR-BT, 2468 were treated with LDR-BT + EBRT, 379 were treated with HDR-BT, and 900 were treated with EBRT. GI toxicity was reported in 14 studies, and GU toxicity was reported in 10 studies. The relative risks of GI and GU toxicities were assessed during follow-up visits. The clinical characteristics and relevant results of all studies are summarized in Table 1 and NOS scores of the 15 studies are shown in Table 2.

3.3. Meta-analysis of GI toxicities between LDR-BT and LDR-BT + EBRT

3.3.1. Acute and late GI toxicity

A meta-analysis of six studies [20,22–24,26,29] revealed that the RR of acute GI toxic complications from LDR-BT was significantly lower than that from LDR-BT + EBRT (2.13; 95% CI, 1.22–3.69; $P = 0.007$) (Fig. 2a).

A meta-analysis of 11 studies [16,19–27,29] revealed that the RR of late GI toxic complications from LDR-BT was significantly lower than that from LDR-BT + EBRT (3.96; 95% CI, 1.23–12.70; $P = 0.02$) (Fig. 2b).

Table 1
Studies characteristics

Study/year	Country	Study design	Time	NCCN risk groups (n)			Treatment group	Sample size	Prescribed dose
				Low	Intermediate	High			
Taniguchi et al. [16], 2020	Japan	RCS	2004–2016	132	140	26	LDR-BT+2D-CRT	120	104Gy+40Gy
							LDR-BT	178	145Gy
Moll et al. [17], 2020	Austria	RCS	2000–2019	477	0	0	LDR-BT	264	145Gy
							3D-CRT/VMAT	213	NA
Tanaka et al. [18], 2019	Japan	PCS	2005–2010	NA	NA	NA	LDR-BT+EBRT	547	NA
							LDR-BT	1792	NA
Tomoki et al. [19], 2018	Japan	RCS	2003–2013	781	1175	260	LDR-BT+3D-CRT/IMRT	955	100Gy+45Gy
							LDR-BT	1261	145Gy/160Gy
Yamazaki et al. [20], 2018	Japan	RCS	2005–2013	194	250	42	LDR-BT+EBRT	68	110Gy+40Gy
							LDR-BT	418	145Gy
							HDR-BT	352	49–54Gy/7–9fr/4–7days
Maki et al. [21], 2017	Japan	RCS	2005–2011	132	147	21	LDR-BT+3D-CRT/IMRT	29	110Gy+40Gy
							LDR-BT	271	145Gy
Katayama et al. [22], 2016	Japan	PCS	2005–2010	NA	NA	NA	LDR-BT+2D, 3D-CRT/IMRT	547	100–110Gy+40–50Gy
							LDR-BT	1791	144Gy
Mukai et al. [23], 2018	Japan	RCS	2014–2017	4	60	41	LDR-BT+3D-CRT/IMRT	60	110Gy+45Gy
							LDR-BT	45	160Gy
Ohashi et al. [24], 2015	Japan	PCS	2005–2007	2057	1836	158	LDR-BT+2D, 3D-CRT/IMRT	547	100–110Gy+40–50Gy
							LDR-BT	1792	144Gy
Sutani et al. [25], 2015	Japan	RCS	2006–2013	364	389	331	LDR-BT	379	160Gy
							2D, 3D-CRT/IMRT	410	60–76Gy/76–78Gy
							LDR-BT+EBRT	295	110Gy+45Gy
Tanaka et al. [26], 2013	Japan	PCS	2004–2008	NA	NA	NA	LDR-BT+EBRT	63	110Gy+45Gy
							LDR-BT	155	145Gy/160Gy
Kalakota et al. [27], 2010	USA	RCS	1997–2006	82	23	5	LDR-BT+3D-CRT/IMRT	48	110Gy+45Gy
							LDR-BT	62	144Gy
Morimoto et al. [28], 2014	Japan	RCS	2008–2010	55	24	54	LDR-BT	37	145Gy
							3D-CRT/IMRT	92	70Gy/70, 74Gy
							HDR-BT	27	45.5Gy/7fr/4days
Zelefsky et al. [29], 2008	USA	RCS	2002–2005	226	107	10	LDR-BT+IMRT	127	110Gy+50.4Gy
							LDR-BT	216	144Gy
Eade et al. [30], 2008	USA	RCS	1998–2004	NA	NA	NA	LDR-BT	158	145Gy
							IMRT	216	74–78Gy

Table 1, continued

Study/year	RV 100 (ml)	RV 150 (ml)	U 200 (ml)	U 150 (ml)	PSA (ng/ml)	HT	Follow-up	Toxicity evaluation	End-points
Taniguchi et al. [16], 2020	0.37 (0.09–0.8)	0.005 (0–0.07)	NA	NA	7.9 (5.7–11.1)	106	7.6 (5.1–10.2) years	CTCAE	GI toxicity
	0.32 (0.08–0.9)	0 (0–0.07)	NA	NA	5.9 (4.9–7.1)	140	6.4 (4.8–8.5) years		
Moll et al. [17], 2020	NA	NA	NA	NA	6.4 (0.6–10)	33	68 (3–181) months	RTOG	GI/GU toxicity
	NA	NA	NA	NA	6.4 (0.3–10)	77	71 (3–192) months		
Tanaka et al. [18], 2019	0.4 ± 0.5	0.0 ± 0.1	0.0 ± 0.0	NA	10.6 ± 5.6	154	60 months	CTCAE	GU toxicity
	0.5 ± 0.6	0.1 ± 0.1	0.1 ± 2.3	NA	7.2 ± 3.1	1101	60 months		
Tomoki et al. [19], 2018	NA	NA	NA	NA	NA	422	7.4 (4.9–9.8) year	CTCAE	GI toxicity
	NA	NA	NA	NA	NA	438	6.5 (4.5–9.1) year		
Yamazaki et al. [20], 2018	NA	NA	NA	NA	7.0 (1.4–46)	NA	90 (12–151) months	CTCAE	GI/GU toxicity
	NA	NA	NA	NA	7.0 (1.4–46)	NA	90 (12–151) months		
	NA	NA	NA	NA	7.0 (1.4–46)	NA	84 (19–216) months		
Maki et al. [21], 2017	0.35 (0 ± 0)	0.02 (0 ± 0.1)	NA	NA	7.0 (2.6–25)	NA	53 (5–99) months	CTCAE	GI toxicity
	0.28 (0 ± 0.4)	0.01 (0 ± 0.1)	NA	NA	7.0 (2.6–25)	NA	53 (5–99) months		
Katayama et al. [22], 2016	0.43 ± 0.53	0.04 ± 0.11	0.01 ± 0.05	NA	10.6 (1.9–42)	390	7 years	CTCAE	GI toxicity
	0.50 ± 0.59	0.05 ± 0.13	0.07 ± 2.27	NA	7.2 (1.6–42)	764	7 years		
Mukai et al. [23], 2018	0.08 ± 0.2	NA	NA	0 ± 0.02	9.0 (4–54.6)	26	28 months	CTCAE	GI/GU toxicity
	0.2 ± 0.3	NA	NA	0 ± 0.12	7.5 (4–20.6)	19	28months		
Ohashi et al. [24], 2015	0.3 (0.0–3.7)	0.0 (0.0–1.2)	0.0 (0.0–0.6)	NA	9.3 (1.9–42)	NA	36 months	CTCAE	GI/GU toxicity
	0.3 (0.0–4.8)	0.0 (0.0–1.5)	0.0 (0.0–92.9)	NA	9.3 (1.9–42)	NA	36 months		
Sutani et al. [25], 2015	NA	NA	NA	NA	NA	103	43 (25–61) months	RTOG	GI/GU toxicity
	NA	NA	NA	NA	NA	208	43 (27–61) months		
	NA	NA	NA	NA	NA	108	45 (27–62) months		
Tanaka et al. [26], 2013	0.11 ± 0.19	NA	NA	NA	12.5 ± 6.1	26	38.3 ± 16.2 months	CTCAE	GI/GU toxicity
	0.08 ± 0.16	NA	NA	NA	7.2 ± 2.4	43	44.2 ± 14.9 months		
Kalakota et al. [27], 2010	0.09 (0–1.39)	NA	NA	NA	6.0 (1.0–41)	16	56 (4–100) months	RTOG	GI toxicity
	0.02 (0–1.31)	NA	NA	NA	6.0 (2.0–26)	2	34 (4–87) months		
Morimoto et al. [28], 2014	NA	NA	NA	NA	8.7 (2.0–337)	NA	19 (5–36) months	CTCAE	GI/GU toxicity
	NA	NA	NA	NA	8.7 (2.0–337)	NA	19 (5–36) months		
	NA	NA	NA	NA	8.7 (2.0–337)	NA	19 (5–36) months		
Zelefsky et al. [29], 2008	NA	NA	NA	NA	NA	43	30 months	CTCAE	GI/GU toxicity
	NA	NA	NA	NA	NA	2	30 months		
Eade et al. [30], 2008	NA	NA	NA	NA	5.2 (0.5–9.8)	NA	48 months	RTOG	GI/GU toxicity
	NA	NA	NA	NA	5.2 (0.4–9.6)	NA	43 months		

RCS, Retrospective Cohort Study; PCS, Prospective Cohort Study; LDR-BT, Low-dose-rate brachytherapy; HDR-BT, High-dose-rate brachytherapy; 2D-CRT, 2-dimensional conformal radiation therapy; 3D-CRT, 3-dimensional conformal radiation therapy; IMRT, Intensity-modulated radiation therapy; VMAT, Volume-modulated arc therapy; CTCAE, Common Terminology Criteria for Adverse Events; RTOG, Radiation Therapy Oncology Group grading; GI toxicity, Gastrointestinal toxicity; GU toxicity, Genitourinary toxicity; NA, Not Available.

Table 2
Details of study quality evaluation via the Newcastle-Ottawa Scale

Study/year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Taniguchi et al. [16], 2020	1	1	1	1	1	1	1	1	1	9
Moll et al. [17], 2020	1	1	1	1	1	1	1	1	1	9
Tanaka et al. [18], 2019	1	1	1	1	1	1	1	1	1	9
Tomoki et al. [19], 2018	1	1	1	1	1	1	1	1	1	9
Yamazaki et al. [20], 2018	1	1	1	1	1	1	1	1	1	9
Maki et al. [21], 2017	1	1	1	1	1	1	1	1	1	9
Katayama et al. [22], 2016	1	1	1	1	1	1	1	1	1	9
Mukai et al. [23], 2018	1	1	1	1	1	1	1	0	1	8
Ohashi et al. [24], 2015	1	1	1	1	1	1	1	0	1	8
Sutani et al. [25], 2015	1	1	1	1	1	1	1	0	1	8
Tanaka et al. [26], 2013	1	1	1	1	1	1	1	0	1	8
Kalakota et al. [27], 2010	1	1	1	1	1	1	1	0	1	8
Morimoto et al. [28], 2014	1	1	1	1	1	1	1	0	1	8
Zelefsky et al. [29], 2008	1	1	1	1	1	1	1	0	1	8
Eade et al. [30], 2008	1	1	1	1	1	1	1	0	1	8

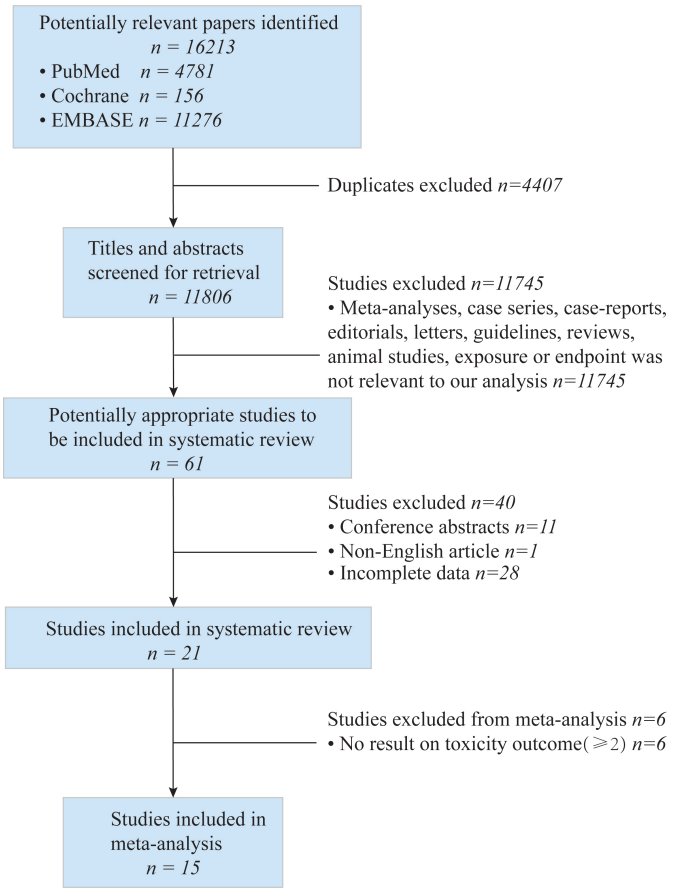

Fig. 1. Study selection. Flow diagram summarising selection of studies that meet inclusion criteria.

3.4. Meta-analysis of GU toxicities between LDR-BT and LDR-BT + EBRT

3.4.1. Acute and late GU toxicity

A meta-analysis of six studies [18,20,23,24,26,29] revealed that there was no significant difference in the RR of acute GU toxic complications between LDR-BT and LDR-BT + EBRT (0.65; 95% CI, 0.23–1.83; $P = 0.41$) (Fig. 3a).

A meta-analysis of six studies [20,23–26,29] revealed that there was no significant difference in the RR of late GU toxic complications between LDR-BT and LDR-BT + EBRT (1.18; 95% CI, 0.85–1.62; $P = 0.32$) (Fig. 3b).

3.5. Heterogeneity analysis of LDR-BT and LDR-BT + EBRT studies

Six studies reporting acute GI toxicity did not present heterogeneity ($P > 0.1$; $I^2 < 50\%$). A random-effect model was selected for the analysis. An independent SA was performed after excluding two studies [22,24]. The four assessed studies showed different results, indicating that our research results were unstable (Table 3). Due to the high heterogeneity among studies reporting late GI toxicity, SA was performed after excluding one article [19]. The other 10 studies showed different results (5.60; 95% CI, 3.63–8.65; $P < 0.001$; $I^2 = 38\%$) (Table 4), indicating that our research results were unstable.

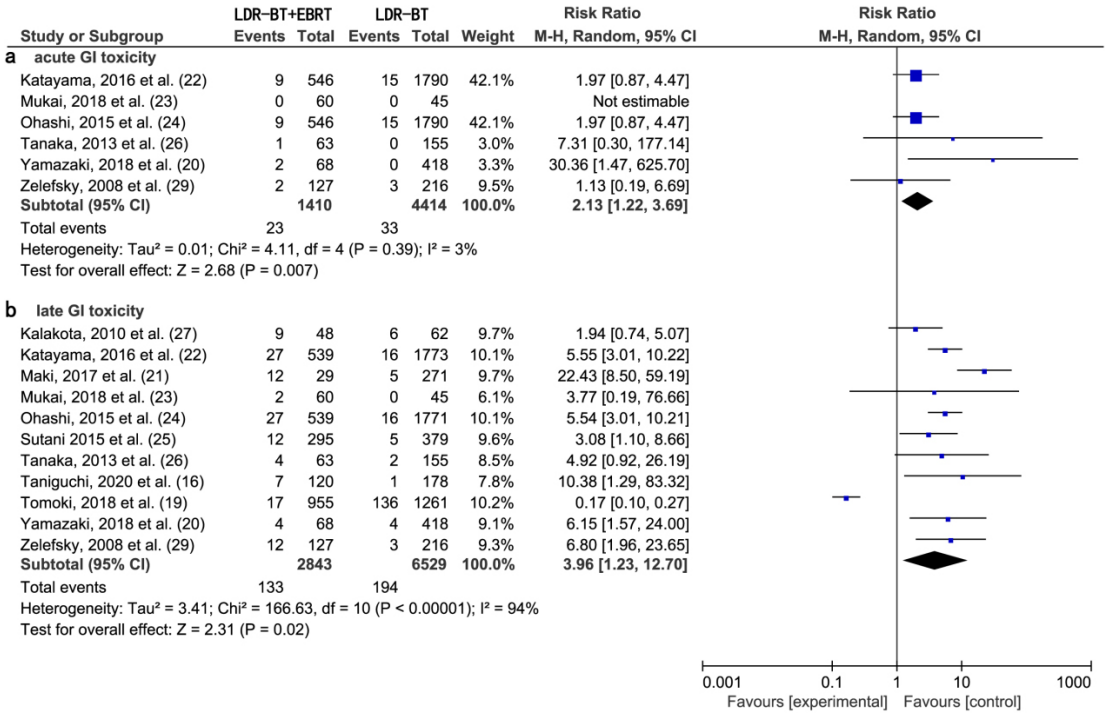

Fig. 2. (a) Forest plot of RR for acute GI toxicity following LDR-BT + EBRT and LDR-BT. (b) Forest plot of RR for late GI toxicity following LDR-BT + EBRT and LDR-BT.

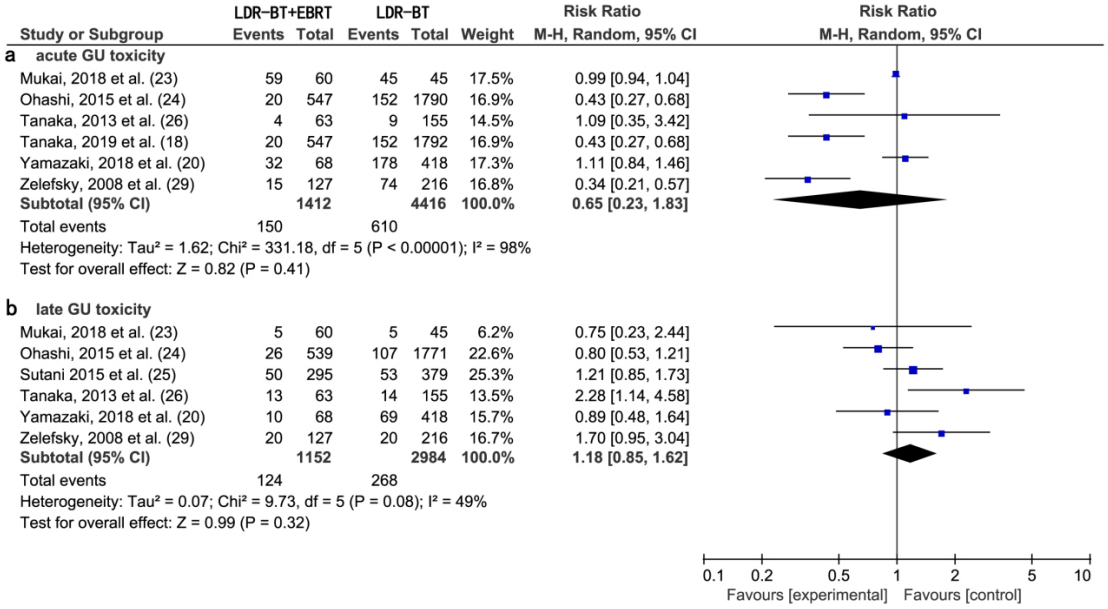

Fig. 3. (a) Forest plot of RR for acute GU toxicity following LDR-BT + EBRT and LDR-BT. (b) Forest plot of RR for late GU toxicity following LDR-BT + EBRT and LDR-BT.

Table 3
Sensitivity analysis (acute GI toxicity)

	RR	95% CI	p	Q (p)	I^2
All studies	2.13	1.22–3.69	0.007	0.39	3%
Selected study omitted					
Yamazaki et al. [20], 2018	1.94	1.13–3.34	0.02	0.8	0%
Katayama et al. [22], 2016	2.58	0.92–7.27	0.07	0.25	26%
Mukai et al. [23], 2018	2.13	1.22–3.69	0.007	0.39	3%
Ohashi et al. [24], 2015	2.58	0.92–7.27	0.07	0.25	26%
Tanaka et al. [26], 2013	2.07	1.11–3.86	0.02	0.32	14%
Zelefsky et al. [29], 2008	2.38	1.21–4.68	0.01	0.31	17%

Table 4
Sensitivity analysis (late GI toxicity)

	RR	95% CI	p	Q (p)	I^2
All studies	3.96	1.23–12.7	$p < 0.00001$	0.02	94%
Selected study omitted					
Taniguchi et al. [16], 2020	3.65	1.07–12.41	$p < 0.00001$	0.04	95%
Tomoki et al. [19], 2018	5.60	3.63–8.65	0.11	$p < 0.00001$	38%
Yamazaki et al. [20], 2018	3.79	1.10–13.13	$p < 0.00001$	0.04	94%
Maki et al. [21], 2017	3.27	1.01–10.59	$p < 0.00001$	0.05	93%
Katayama et al. [22], 2016	3.83	1.03–14.23	$p < 0.00001$	0.03	94%
Mukai et al. [23], 2018	3.97	1.18–13.35	$p < 0.00001$	0.03	95%
Ohashi et al. [24], 2015	3.83	1.03-14.23	$p < 0.00001$	0.04	94%
Sutani et al. [25], 2015	4.08	1.14–14.64	$p < 0.00001$	0.03	95%
Tanaka et al. [26], 2013	3.88	1.13–13.38	$p < 0.00001$	0.03	95%
Kalakota et al. [27], 2010	4.29	1.18–15.57	$p < 0.00001$	0.03	95%
Zelefsky et al. [29], 2008	3.75	1.08–13.08	$p < 0.00001$	0.04	94%

3.6. Meta-analysis of GI and GU toxicities between LDR-BT and EBRT

3.6.1. Acute and late GI toxicity

A meta-analysis of two studies [28,30] revealed that there was no significant difference in the RR of acute GI toxic complications between LDR-BT and EBRT alone (0.75; 95% CI, 0.21–2.74; $P = 0.66$) (S: Fig. 4a). The number of studies for this analysis was insufficient for an SA. And a meta-analysis of three studies [17,25,30] revealed no significant difference in the RR of late GI toxic complications between LDR-BT and EBRT alone (0.50; 95% CI, 0.10–2.48; $P = 0.39$) (S: Fig. 4b). The number of studies for this analysis was insufficient for an SA.

3.6.2. Acute and late GU toxicity

A meta-analysis of two studies [28,30] revealed that the RR of acute GU toxic complications from EBRT was significantly lower than that from LDR-BT alone (2.32; 95% CI, 1.29–4.15; $P = 0.005$) (S: Fig. 5a). The number of studies for this analysis was insufficient for an SA. And a meta-analysis of three studies [17,25,30] revealed that the RR of late GU toxicity from EBRT was significantly lower than that from LDR-BT alone (2.38; 95% CI, 1.27–4.44; $P = 0.007$) (S: Fig. 5b).

3.7. Meta-analysis of GI and GU toxicities between HDR-BT and LDR-BT

3.7.1. Acute GI toxicity and GU toxicity

A meta-analysis of two studies [20,28] revealed no significant difference in the RR of acute GI toxic complications between HDR-BT and LDR-BT alone (4.14; 95% CI, 0.84–20.40; $P = 0.08$) (S:

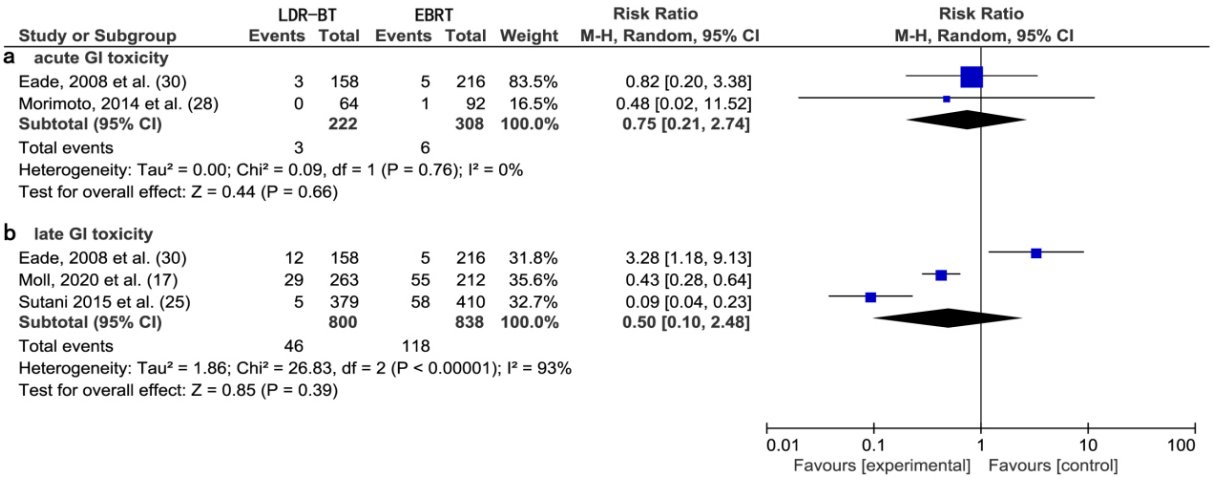

Fig. 4. (a) Forest plot of RR for acute GI toxicity following LDR-BT and EBRT. (b) Forest plot of RR for late GI toxicity following LDR-BT and EBRT.

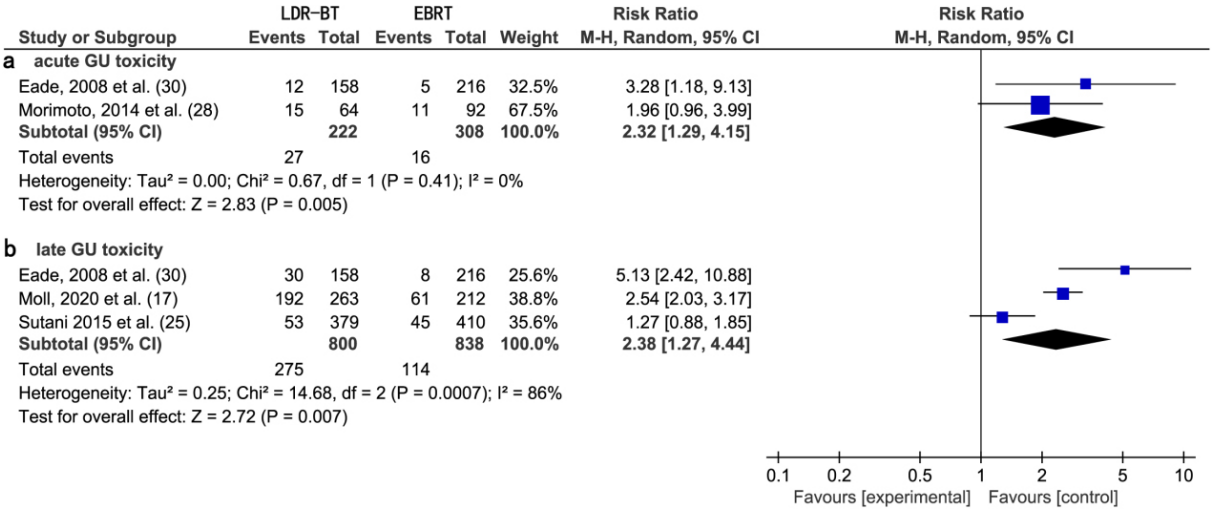

Fig. 5. (a) Forest plot of RR for acute GU toxicity following LDR-BT and EBRT. (b) Forest plot of RR for late GU toxicity following LDR-BT and EBRT.

Fig. 6a). The number of studies for this analysis was insufficient for an SA. And a meta-analysis of two studies [20,28] revealed that the RR of acute GU toxicity from HDR-BT was significantly lower than that from LDR-BT (0.30; 95% CI, 0.23–0.40; $P < 0.001$) (S: Fig. 6b). The number of studies for this analysis was insufficient for an SA.

4. Discussion

With the results of this meta-analysis, we evaluated the significance of RRs of GI toxicities and GU toxicities in studies by comparing the following therapies: (A) LDR-BT and LDR-BT + EBRT, (B) LDR-BT and EBRT alone, (C) EBRT and LDR-BT + EBRT, and (D) HDR-BT and LDR-BT alone. The

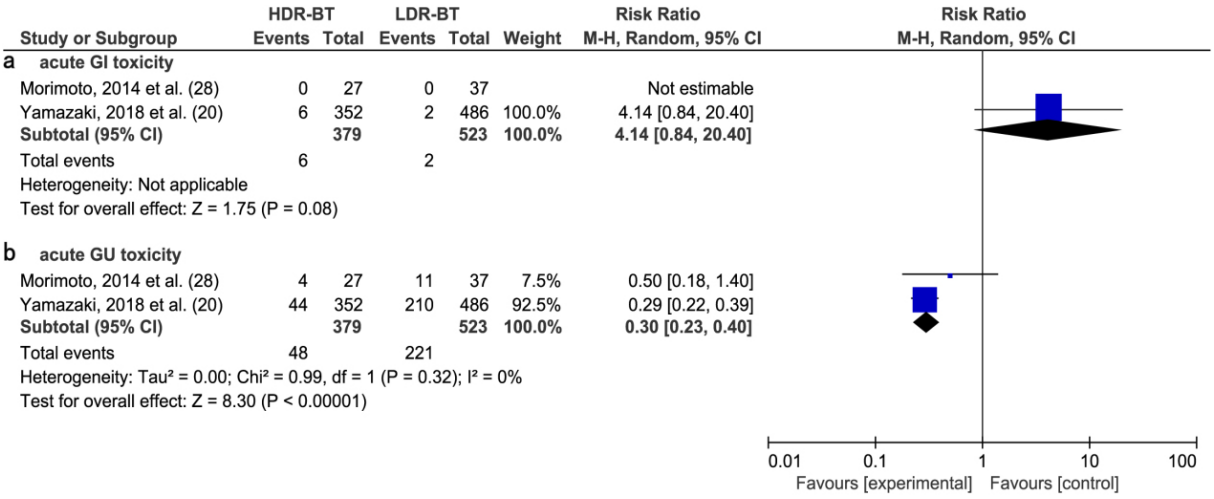

Fig. 6. (a) Forest plot of RR for acute GI toxicity following HDR-BT and LDR-BT. (b) Forest plot of RR for acute GU toxicity following HDR-BT and LDR-B.

RRs for acute and late GI from LDR-BT were significantly lower than those from LDR-BT + EBRT. However, the RRs for acute toxicities and late GU toxicities were not significantly different between LDR-BT and LDR-BT + EBRT. The RRs for acute toxicities and late GU toxicities for EBRT were significantly better than those for LDR-BT. However, the RRs for acute toxicities and late GI toxicities were not significantly different between LDR-BT and EBRT. We also found that HDR-BT was related to a lower incidence of GU toxicities than LDR-BT. These results demonstrate that BT with and without EBRT can result in both acute and late GI toxicities and GU toxicities with localized prostate cancer. Moreover, the RRs of acute and late GI toxicities of BT + EBRT were significantly higher than those for BT.

The varied RT doses in studies must be considered when comparing the RRs of GI and GU toxicities between different therapies [31]. BT + EBRT may increase the RRs of GI and GU toxicities because of the combined higher RT dose [32–34]. Increased urinary complications result from a high dose from EBRT during BT. Many doctors may administer a high BT dose to compensate for soft tissue edema or seed placement [35,36]. Uncertainty factors of needle and seed placement and the resulting induced trauma can lead to GU toxicity [37–40]. Substantially lower occurrences of acute urinary toxicities have been achieved using a combined BT + EBRT regimen [41], which may be related to different implant prescription doses and/or a different application of EBRT. Based on our analysis, the implant prescription dose and application of supplemental EBRT had no significant effect on GU toxicity incidence (Fig. 3). These results indicate that additional clinical studies are needed to further investigate the effect of various BT treatments on GU toxicity.

Testosterone levels may decline as a result of hormone therapy (HT) on urinary toxicity [42,43]. HT itself may affect urinary symptoms: this must be considered when comparing both the tumor outcome and toxicity of BT and BT + EBRT [44–46]. In a previous study, BT with hormonotherapy increases the progression-free survival rates for men with localized prostate cancer [47]; however, the study did not evaluate GU toxicity. In one study evaluating EBRT for men with localized prostate cancer, HT increased the risk of grade 2 acute GU toxicities significantly [48,49]. A meta-analysis reported that HT combined with RT could decrease micro-metastases and delay biochemical relapse; however, both RT and HT

have a greater toxicity than RP [50]. HT was a probable confounding factor in our study because of the differences in its application and duration between the 15 cohort studies.

Large, population-based cancer patient cohort studies show that BT + EBRT is associated with a significantly higher prostate cancer-specific survival and similar overall survival (OS) than surgery or EBRT [51]. BT + EBRT can delay disease progression and result in a similar OS and higher cancer-specific survival with acceptable toxicity than RP [52]. Furthermore, BT + EBRT may lead to increased GI toxicity while decreasing the RR of GU toxicity. Kishan et al. [53]. reported a better prognosis associated with EBRT + BT than RP or EBRT alone. BT + EBRT might be a reasonable treatment for men with high T stages or high Gleason scores. Some studies have shown a relatively high incidence of GI toxicity with BT + EBRT [54]. Although the incidence of high-grade GI toxicities was low, all people were treated with supplemental EBRT [55,56]. Our pooled results showed that localized prostate cancer treated with BT had significantly lower RRs for acute and late GI toxicities than those treated with BT + EBRT. Our BT-related GI toxicity results are similar to those of Wang et al. [50] who reported that BT + EBRT leads to a high incidence of post-radiotherapy GI toxicity. The greater RR of GI toxicity for those patients receiving EBRT compared to BT + EBRT may be attributed to an increase in the exposure of the rectum and surrounding tissue to radiation.

Previous studies reported a 15 years disease-free survival rate of 80.4% after treatment of men with localized prostate cancer with BT [57,58]. Another studies reported a 5 years and 10 years OS rate of 94% and 84%, respectively, among similar patients [59]. These findings confirm the long-term efficacy of BT treatment for localized prostate cancer. Kee et al. [60]. Published a meta-analysis of clinical randomized control trials, which revealed a significantly higher 5 years biochemical progression-free survival with ^{125}I-BT than with EBRT supplement. However, there was no significant increase in the 5 years survival or OS for men with grade 3 late GI and GU toxicities. We included recent data in our meta-analysis and found significantly lower RRs of GU toxic complications for men treated with EBRT than with BT, although the incidence of GI toxic complications were similar between two therapies. Our observation that BT can increase late GU toxicity is consistent with that of Rodda et al. [54]. In the comparison of toxicity between HDR-BT and LDR-BT, HDR-BT significantly reduced the incidence of acute GU toxic complications. The radiotherapy dose of an LDR-BT implant seeds is delivered over a 6-month period compared to a 10–15 minute exposure for HDR-BT. As a result, LDR-BT treatment may increase the incidence of acute GU toxic complications than HDR-BT [61,62]. These observations indicate that improving BT radiotherapy regimens, including HDR-BT [63,64], can decrease toxicity and improve the quality of life.

The literature search and screen of this meta-analysis were strict, the included studies were comprehensive, and outcomes were highly credible. However, our analysis has several limitations: (A) the total number of included studies was small (< 10), which precluded an assessment of publication bias; (B) the studies had different populations in terms of T stage, Gleason score, and initial risk stratification-nevertheless, this might be relevant to effective tumor control and patients survival outcomes; (C) the included studies contained insufficient data on HT-related toxicity, radiotherapy volumes and doses, and prostate risk groups; (D) comprehensive subgroup analyses could not be performed; (E) two toxicity scales were used (CTCAE and RTOG), which may have confused the interpretation of our results; (F) there was no uniform definition of time points for acute and late toxicities among the studies; (G) Toxicity data for individual therapies were not available in the combination treatment group, so the toxicity of individual therapies could not be determined, and overlapping effect may not be resolved; (H) There was some heterogeneity with outcomes, but it was accounted for using sensitivity analyses for our study.

5. Conclusions

Our findings implied that BT with and without EBRT can result in both acute and late GI toxic and GU toxic complications in men with localized prostate cancer, with LDR-BT leading to a poorer urinary function than EBRT. The results of this study reveal the need to prevent GI and GU toxic complications after multiple forms of radiotherapy in the future. Prospective clinical studies are needed to verify and expand on our results. When making decisions for treating local prostate cancer, clinicians should balance the effectiveness of different radiotherapies with their safety depends on the actual clinical characteristics.

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Conflict of interest

None to report.

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