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Critical Review

Outcomes and Toxicities After Treatment for Men Diagnosed With Localized Prostate Cancer in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis

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Purpose: Current management for clinically localized prostate cancer in low- and middle-income countries (LMICs) includes surgery, external beam radiation therapy (EBRT), and brachytherapy either alone or in combination, with plus or minus hormone therapy. The toxicity profiles and oncological outcomes of these treatment modalities vary. This systematic review and meta-analysis aimed to determine the prevalence of treatment-related outcomes and toxicities for men diagnosed with localized prostate cancer in LMICs.

Methods and Materials: The review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Cochrane Library, Embase, and Medline were searched for eligible articles. Meta-analysis was performed with Review Manager version 5.4.1 using a random effects model at a 95% confidence interval.

Results: A total of 2,820 patients were analyzed from 24 articles that met the inclusion criteria. Following 3-dimensional conformal radiation therapy (3D-CRT), the most common clinician-reported toxicities were acute skin grade 1, acute genitourinary grade 1, acute gastrointestinal grade 1, and late gastrointestinal grade 1, with 46%, 29%, 24%, and 18%, respectively. Acute and late genitourinary grade 3 and gastrointestinal grade 3 toxicities were below 3% with no grade 4 toxicities reported after 3D-CRT. In the brachytherapy group, the prevalence of acute genitourinary grade 1 toxicity was 19%. Perioperative rectal injury was the least prevalent (2%) after retropubic radical prostatectomy. Following 3D-CRT, the 5-year overall survival rate was 87%, and for the combined brachytherapy and EBRT group, it increased to 96%. The prevalence of 5-year biochemical failure following EBRT and brachytherapy was 18% and 30%, respectively. The 4- and 3-year biochemical failure after radical prostatectomy and combined EBRT with brachytherapy were 22% and 2%, respectively.

Conclusions: This systematic review and meta-analysis indicate that in LMICs, EBRT, brachytherapy, and radical prostatectomy, either alone or in combination has an excellent potential for localized prostate cancer control with low toxicities and good oncological

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outcomes. Results of treatment-related toxicities and outcomes can support policymakers, patients, and clinicians on informed decision-making to strengthen prostate cancer care in the region. However, efforts are required to improve early detection, treatment accessibility, regular post-treatment follow-up care, consistent quality assurance practices, and staff continues development to help minimize treatment toxicities and improve outcomes of localized prostate cancer in LMICs.

Introduction

The global burden of prostate cancer is increasing, with most new cases and prostate cancer-related deaths occurring in low- and middle-income countries (LMICs). In 2020, there were 650,195 new prostate cancer cases in LMICs with 237,032 deaths.[1] Globally, it is projected that the number of men diagnosed with prostate cancer will double from 1.4 million in 2020 to 2.9 million by 2040, with LMICs estimated to record the highest number of cases.[2] In most LMICs, prostate cancer is often underdetected or diagnosed at advanced stages because of barriers such as lack of awareness, lack of targeted screening programs, limited access to pathology services, and poor follow-up data.[2,3] Interventions to improve prostate cancer outcomes in LMICs need to involve all relevant stakeholders to ensure early detection, accurate diagnosis, timely treatment, and optimal follow up to improve the experiences of men diagnosed with prostate cancer and quality of life after treatment.[2]

Treatment options for localized prostate cancer in most LMICs typically include radical retropubic prostatectomy, external beam radiation therapy (EBRT), brachytherapy, and hormone therapy, either alone or in combination.[4] Radiation therapy is critical for both curative and palliative care. Currently, most LMICs have switched from 2-dimensional to 3-dimensional conformal radiation therapy (3D-CRT), and high-precision techniques such as intensity modulated radiation therapy, volumetric arch therapy, and stereotactic body radiation therapy.[5,6] Even though high dose-rate brachytherapy is available, low dose-rate is most commonly used.[7]

Numerous cancer-related outcomes, such as overall survival, metastasis, biochemical failure, and prostate cancer-specific death, have been considered in the planning of prostate cancer treatments.[8] Equally important are gastrointestinal, genitourinary, and skin toxicities because of the location of the prostate.[9,10] Systematic reviews of outcomes and toxicities of localized prostate cancer treatments have been extensively studied.[9,11-17] However, these studies did not distinguish between high-income countries' (HICs) data from LMICs data making it difficult to make policy judgments for LMICs. A systematic review that focused on Africa alone indicated that men diagnosed with localized prostate cancer survive longer; however, the finding was not extensively explored because of the lack of meta-analysis and outcomes stratified by treatment.[18] This systematic review and meta-analysis aimed to determine the prevalence of treatment-related outcomes and toxicities of men diagnosed with localized prostate cancer in LMICs.

Method

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024486632).

Eligibility criteria

The review was focused on men with clinically diagnosed localized prostate cancer. Localized prostate cancer was defined as non-metastatic lesions, that is, tumors confined to the prostate gland with or without extra-prostatic invasion and without regional lymph node involvement or distant metastasis. Studies from LMICs categorized by the World Bank Group into low-income countries [those with a gross national income (GNI) per capita of $1135 or less], lower-middle-income countries (those with a GNI between $1136 and $4465), and upper-middle-income countries (those with GNI between $4466 and $13,845) were considered.[20] All definitive treatments for localized prostate cancer were considered; however, non-English publications were excluded.

Data source

Cochrane Library, Embase, and Medline were searched for eligible articles. These electronic databases were used because of their continuous update with new publications. Hand searches of reference lists of included studies and other systematic reviews were performed for additional relevant articles.

Search strategy

An initial search strategy was developed in Cochrane Library and adapted in Medline and Embase. Terms

associated with the following phrases: "prostate neoplasm," "prostate cancer treatment," and "low- and middle-income countries" were used for the search. Boolean operators "AND" and "OR" were used to combine search terms in free text search, titles, abstract, and medical subject headings. Two reviews were used to create the search terms.[17,21] The searches were done on 2 February 2024 and rerun on 24 February 2024 (see Appendix E1).

Study selection

All citation hits obtained from the electronic database searches were exported to EndNote Version 20 for management. After deduplication, titles and abstracts were screened for relevant articles guided by the study's eligibility criteria. The process was executed by 2 independent reviewers (D.K-M. and K.A.K.) who reconciled the screened results to obtain the full-text articles. Articles that did not meet the inclusion criteria were excluded with justification (see Fig. 1). Any differences that arose between the 2 review authors were settled by dialog and when a consensus was not reached A.D. and Y.A.W. were consulted.

Data extraction

A data extraction form was generated in Excel with the following themes: study characteristics (author, publication year, setting, study objective, study design, sample size, age group, treatment type, assessment tool, follow-ups, risk groups, staging, Gleason score), survival, mortality, metastasis, biochemical failure, acute and late genitourinary and gastrointestinal toxicities. For each study, data were extracted by 2 reviewers (D.K-M. and A.D.). Accuracy and consensus were checked by a third reviewer (Y.A.A.).

Quality assessment

Two review authors (D.K-M. and A.D.) assessed the quality of the included studies. Disagreements were resolved through discussion. Critical Appraisal Skills Program and the Joanna Briggs Institute-specific study design checklist were used to appraise included studies.[22-24] Quality assessment scores equal and below 60% were considered low quality and vice versa. All included studies had high (greater than 74%) quality (see Appendix E2).

Data analysis

Meta-analysis was performed using a random effects model at 95% confidence intervals (95%-CIs).[25] Effect sizes were generated from the pooled prevalence of the individual studies. Standard errors were estimated based on equation 1 where P is the sample proportion and n represents the sample size.[26]

$$SE = \sqrt{(p\ x\ (1-p))/n} \quad (1)$$

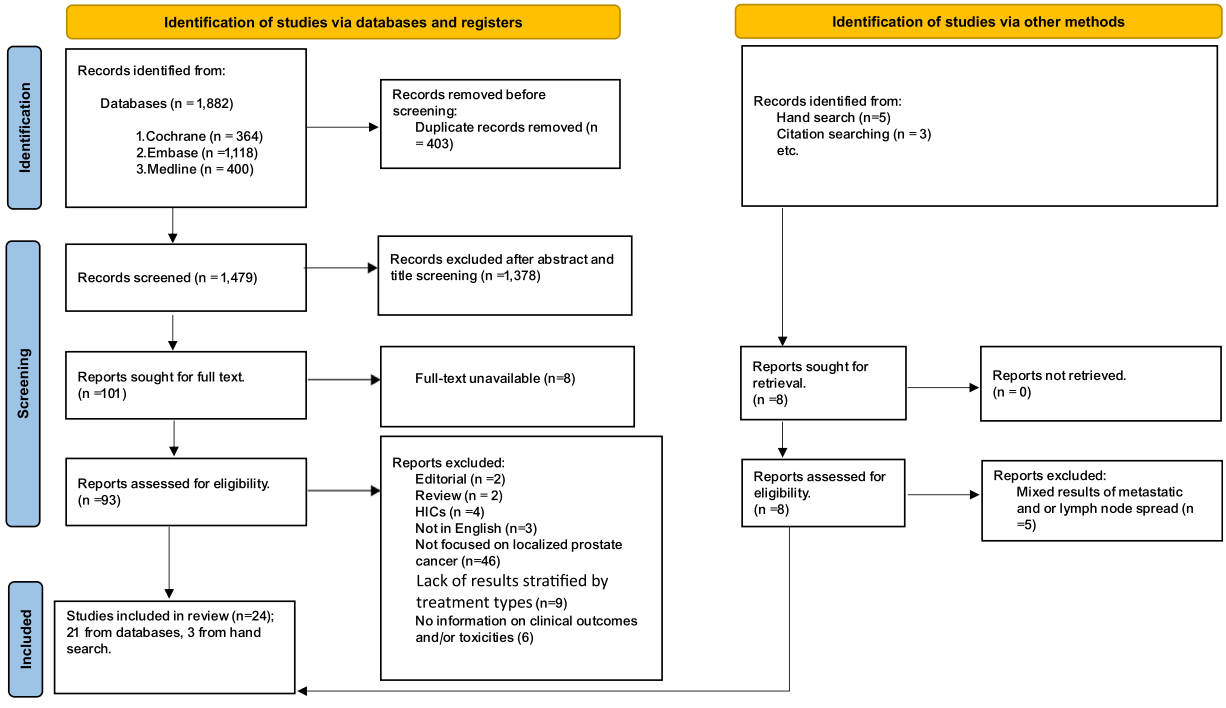

Figure 1 PRISMA flow diagram.

Study heterogeneity was assessed using the I^2 index and categorized as follows: "no heterogeneity (0%)"; "low heterogeneity (25%-50%)"; "moderate heterogeneity (51%-75%)"; "high heterogeneity (>75%)."[27] Heterogeneity was considered significant at probability value of 0.05. Forest plots and tables were generated for the visualization of results. The meta-analysis was performed in Review Manager (RevMan) version 5.4.1.

Results

Study selection

Searches from electronic databases yielded 1882 references. After eliminating 403 duplicates, 1479 references remained for the title and abstract screening. Guided by the eligibility criteria, 1378 articles were excluded. Eight articles could not be retrieved; hence, 93 full-text articles were assessed. Twenty-one articles were eligible with 3 additional papers from hand search. Finally, a total of 24 records reporting on outcomes and toxicities after treatment of men diagnosed with localized prostate cancer were included in this review (see Fig. 1).

Characteristics of included studies

The study designs of the included studies were as follows: 2 clinical trials[28,29]; 20 cohort studies (15 retrospective[30-44] and 5 prospective[45-49]); one cross-sectional study[50]; and one case series.[51] The cumulative sample size of the included studies was 2820 which included: 1862,948, and 10 localized prostate cancer patients treated with radiation therapy, radical prostatectomy, and cryotherapy, respectively. Nine studies used 3D-CRT,[29,32,36,37,40-42,46,50] intensity modulated radiation therapy (IMRT) was used in 2 studies,[30,50] 2 studies used stereotactic body radiation therapy (SBRT),[28,43] and 2-Dimensional radiation therapy (2D-RT) was used in 2 studies.[32,36] High-dose-rate (HDR) brachytherapy was used in 3 studies[29,35,36] and 2 studies used low-dose-rate (LDR) brachytherapy.[31,48] Robotic-assisted radical prostatectomy (RARP) was used in 2 studies[38,39] and 5 studies used retropubic radical prostatectomy (RRP).[35,44,45,47,49] Three studies combined EBRT with brachytherapy.[34,35,48] All studies provided 5%-97% of their included participants with hormonal treatment except 5 studies that did not report on hormonal therapy[38,44,48,49,51] (see Table 1). The included studies were conducted across 11 LMICs, namely: Brazil (n = 7)[29,33,34,36,38,46,51]; India (n = 4)[28,30,32,39]; Ghana (n = 3)[47,48,50,46]; Pakistan (n = 2)[42,44]; Serbia (n = 2)[40,45]; Iran (n = 1)[37]; Malaysia (n = 1)[43]; Peru (n = 1)[35]; Puerto Rico (n = 1)[31]; Russia (n = 1)[49]; and Indonesia (n = 1)[41] (see Fig. 2).

Period of follow-ups

The average follow-up time was less than 5 years; however, 2 studies followed patients for 10 years and above,[32,36] while the other 2 studies followed patients for just 12 and 15 months.[45,51] Acute toxicity was measured within 90 days from the start of treatment and late toxicity beyond 90 days post-treatment in 9 studies.[28,30,35,36,42,43,46,48,51] In one study, acute toxicity was measured within 120 days from the start of treatment and late toxicity beyond 120 days post-treatment.[38] Another study measured acute toxicity within 180 days from the start of the treatment and late toxicity beyond 180 days post-treatment[31] (see Table 1).

Clinician-reported toxicity assessment tools

Three assessment tools were used to measure the clinician-reported outcomes: 8 studies used Radiation Therapy Oncology Group (RTOG)[29,30,32,34,40,42,43,46]; 4 studies used the Common Terminology Criteria for Adverse Events (CTCAE)/National Cancer Institute Common Toxicity Criteria (NCI CTC) version 4.0.[28,31,35,48] Only 2 studies used Clavien-Dindo classification[38,51] (see Table 1).

Patient-reported toxicity assessment tools

There were 5 patient-reported toxicity assessment tools used. Four of the included studies used the International Prostate Symptom Score (IPSS).[28,29,46,48] Two studies used the International Index of Erectile Function (IIEF-15/16).[47,48] The Expanded Prostate Cancer Index Composite (EPIC) Questionnaire was also used in 2 studies.[45,46] Only one study used the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ) C30.[28] Medical Outcome Study 8-item Short-form Health Survey (SF-8) was also used in only one study[45] (see Table 1).

Outcomes and toxicities following EBRT

Acute gastrointestinal toxicities

Four studies consisting of 340 patients who underwent 3D-CRT provided data on acute gastrointestinal toxicity.[32,40,42,46] The pooled prevalence of acute gastrointestinal grades 1-3 toxicities for patients that received 3D-CRT was 24% (95% [CI, 8%-41%]; $I^2 = 94\%$, $P < .00001$), 17% (95% [CI, 3%-31%]; $I^2 = 95\%$, $P < .00001$), and 1% (95% [CI, 0%-3%] $I^2 = 9\%$, $P = .33$), respectively (see Table 2).

Table 1 Characteristics of Included Studies

(Authors, Year); Country	Objective(s)	Study design	Treatment	Sample size	Hormonal therapy (%)	Follow-up mean/median (SD or range)	Period of toxicity (d)	T stage (%)	PSA mean/median (SD or range)	Gleason score (%)	Risk group (%)	Age mean/median (SD or range)	Tool	Extracted outcome
(Stankovic et al., 2016); Serbia	To estimate the incidence of acute and late lower GI toxicity in patients with localized PCa	Retrospective cohort	EBRT (3D-CRT) (72 Gy, 2 Gy daily)	94	17	27 (6-54)	Acute < 90 Late > 90	T1 (53.2) T2 (46.8)	9.884 ± 3.186	≤6 (72.3) 7 (27.7)	L (56.4) I (43.6)	71 (56-81)	RTOG	GI and GU toxicities
(Daniels et al., 2023); Ghana	To assess the biochemical outcomes of patients treated for localized PCa	Cross-sectional	EBRT (3D-CRT) ≤72 Gy, (IMRT) 74-78 Gy	122	76	31.3 (12-60)	N/A	T1 (14.8) T2 (75.4) T3 (9.8)	NR	≤6 (23.6) 7 (32.7) 8-10 (43.7)	L (8.0) I (10.9) H (81)	67.6 (6.2)	N/A	BF
(Pei Yuin et al., 2023), Malaysia	To evaluate the correlations between the biochemical efficacy, and treatment toxicity in SBRT for localized PCa	Retrospective cohort	EBRT (SBRT) 24-35 Gy	49	81.6	45.4 (23.2-71.0)	Acute < 90 Late > 90	T1 (12.3) T2 (71.4) T3 (16.3)	11.2 (0.1-625.0)	6 (28.6) 7 (46.9) ≥8 (24.5)	L (10.2) I (26.5) H (63.3)	68 (48-85)	RTOG	BCR-FS, DMFS, OS GU, GI toxicities
(De et al., 2010); India	To assess the feasibility of dose escalation to prostate and/or seminal vesicles	Prospective cohort	EBRT (IMRT) 76 Gy	40	72.5	NR	Acute < 90	T1 (12.5) T2 (62.5) T3 (25)	16.3 (11-19)	≤6 (30.0) 7 (40.0) 8-9 (30.0)	I (50) H (50)	71 (51-80)	RTOG	Acute GI/GU toxicities
(Engineer et al., 2010); India	To evaluate the changing trends of treatment outcomes of PCa patient	Retrospective cohort	EBRT (2D-RT, 3D-CRT) 45-70 Gy	174	69.5	25 (2-195)	NR	T1 (0.6) T2 (28.7) T3 (59.8) T4 (10.9)	18 (0-450)	2-6 (19.5) 7 (23.0) 8-10 (15.5)	L (8.0) I (10.9) H (81.0)	65 (41-85)	RTOG	bDFS, DFS, OS, GU, GI, skin toxicities
(Faustino et al., 2022); Brazil	To evaluate the toxicity associated with a short course dose escalated HFRT in PCa patients.	Prospective cohort	EBRT (3D-CRT) 60-66 Gy	111	81	46 (6-61)	Acute < 90 Late > 90	T1 (26.1) T2 (38.7) T3 (35.1)	13 (2-94)	≤6 (18.9) 7 (67.0) 8-9 (12.7)	L (12) I (32) H (56)	69 (59-76)	RTOG IPSS EPIC	OS, BF, GU, GI toxicities, QoL (urinary function)
(Mallick et al., 2020); India	To determine the rates of acute GI and GU according to (NCI CTC) v4 & biochemical control	Clinical Trial	EBRT (SBRT, VMAT) 35-50 Gy	30	96.7	41.5 (28-55)	Acute < 90	T2 (40) T3 (60)	17.05 (7.52-60.00)	6 (26.7) 7 (50.0) 8-10 (23.3)	L (3.3) I (30.0) H (66.7)	70 (52-79)	IPSS NCICTC EORTC QLQ C30 PR25	BF, Late & Acute toxicity QoL (urinary function)
(Rakhsha et al., 2015); Iran	To identify the 5-year bPFS and related prognostic and predictive factors of localized PCa	Retrospective cohort	EBRT (2D, 3D-CRT)	192	79.7	31 (14-81)	N/A	T2 (100)	22.8 (1.8-455)	2-7 (64.6) 8-10 (35.4)	L (3.6) I (27.1) H (69.3)	67 (48-87)	N/A	BFS
(Supit et al., 2013); Indonesia	To describe the survival outcome and prognostic factors for localized PCa	Retrospective cohort	EBRT (3D-CRT + IMRT) 60-79 Gy	96	91.6	61 (24-169)	N/A	T1 (50.0) T2(34.3) T3 (15.6)	24.5 (1.4-732)	2-6 (10.4) 7 (52.1) 8-10 (35.4)	L (3.1) I (26.0) H (70.8)	69 (50-82)	N/A	BFS, OS
(Zamir et al., 2017): Pakistan	To evaluate local toxicity and biochemical disease-free survival (bDFS) in PCa	Retrospective cohort	EBRT (3D-CRT) 74 Gy	53	96.2	NR (3-24)	Acute < 90 Late > 90	T2 (26.4) T3(28.3) T4 (45.3)	NR (NR-50)	≤6 (5.7) 7 (28.3) 8-10 (66.0)	L (3.8) I (9.4) H (86.8)	NR (45-70)	RTOG	BF, GU, GI, Skin toxicities
(Pellizzon et al., 2011)	To assess toxicity and preliminary biochemical outcome of unfavorable risk PCa patients.	Prospective Observational	EBRT (3D-CRT) 45 + BT (HDR) 30	39	38.5	42.5 (22-69)	Acute < 90 Late > 90	T1 (66.7) T2 (33.3)	12.0 (1.9-48.7)	≤6 (7.7) 7 (71.8) ≥8 (20.5)	I (41.0) H (59.0)	69 (58-80)	IPSS RTOG/ EORTC	BF, OS, DSS, urinary function GU toxicity
(Pellizzon et al., 2008); Brazil	To evaluate the prognostic factors for patients with local or locally advanced PCa	Retrospective cohort	EBRT (2D, 3D-CRT) 40 Gy+ BT (HDR) 18 Gy	209	48.3	62.9 (24-120)	N/A	T1 (45.5) T2(43.5) T3 (11.0)	10.5(4-175)	≤6 (70.8) 7 (19.6) ≥8 (9.6)	L (36.8) I (31.2) H (32.2)	68.0 (47-83)	N/A	OS, Death

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Table 1 (*Continued*)

(Authors, Year); Country	Objective(s)	Study design	Treatment	Sample size	Hormonal therapy (%)	Follow-up mean/median (SD or range)	Period of toxicity (d)	T stage (%)	PSA mean/median (SD or range)	Gleason score (%)	Risk group (%)	Age mean/median (SD or range)	Tool	Extracted outcome
(Franca et al., 2007); Brazil	To report the result of brachytherapy with Iodine-125 seeds, used in combination with EBRT in localized PCa	Retrospective cohort	EBRT + BT 110 Gy BT 144 Gy	90	50	70 (25-108)	120	T1 (14.5) T2 (85.5)	13.65 (3.2-70)	2-6 (80.0) >6 (20.0)	L (37.0) I (38.0) H (25.0)	68 (46-90)	RTOG	BFS, Death, GU, GI toxicity
(Mensah et al., 2016); Ghana	To report clinical outcomes and complications identified in the first 90 patients treated with BT	Prospective cohort	BT (LDR) 160 GY EBRT + BT 110 Gy	90	NR	58 (18-74)	Acute < 90	T1 (31.1) T2 (63.3) T3 (5.5)	13 (2.1-133)	2-6 (63.3) 7 (28.8) 8-10 (7.8)	L (24.4) I (48.8) H (26.7)	58 (18-74)	CTCAE IIEF-15 IPSS	BF, GU, GI toxicity, Death,
(Echevarria et al., 2017); Puerto Rico	To investigate LDR-BT for the treatment of PCa in a low-resource setting	Retrospective cohort	BT (LDR) 145 Gy	191	86	26 (1-64)	Acute < 180	T1 (79) T2 (21)	5 (0.6-21.8)	≤6 (93.7) 7 (5.8) 8 (0.5)	L (70.0) I (24.0) H (1.0)	66 (46-84)	CTCAE	BFS, GU, GI toxicity,
(Galdos-Bejar et al., 2022); Peru	To compare BF and toxicity associated with surgical treatment and EBRT	Retrospective cohort	EBRT+ BT(HDR) 265-290 Gy vs RRP	130 419	73.9 29.4	33.81 (±20.3) 40.01 (±23.13)	Acute < 90	T2 (51.5) T3 (48.5) T2 (55.6) T3 (44.4)	NR	≤6 (5.4) 7 (56.2) ≥8 (38.4) ≤6 (2.9) 7 (65.6) ≥8 (31.5)	I (46.9) H (53.1) I (54.2) H (45.8)	NR	CTCv5	BF, toxicity
(Dragićević, 2010); Serbia	To evaluate the health-related quality of life (HRQOL)	Prospective cohort	RRP vs BT 145 Gy	96 88	3.1 14.8	NR (1-12)	N/A	T1 (61.5) T2 (32.3) T3 (6.3) T1 (70.5) T2 (27.3)	9.0 (1.30-60.0) 6.3 (2.0-22.3)	≤6 (18.8) 7 (35.4) ≥8 (45.8) ≤6 (46.6) 7 (48.9) ≥8 (0.1)	NR	66 (51-79) 69 (52-84)	EPIC SF-8	HRQOL
(Ferreira et al., 2015); Brazil	To analyze the survival of PCa	Retrospective cohort	RP vs BT 144 Gy	65 64	1.5 17.0	26.6 (NR) 56.1 (NR)	N/A	T1 (32.4) T2 (59.9) T3 (6.1) T1 (40.6) T2 (54.8) T3 (4.6)	0.01 (NR) 0.14 (NR)	2-6 (73.8) 7 (21.6) 8-9 (4.6) 2-6 (75.0) 7 (20.4) 8-9 (1.5)	L ((63.1) I (26.2) H (10.7) L (64.1) I (29.6) H (6.3)	62.5 (48-74) 73 (54-85)	N/A	Survival, BF, Death
(Kyei et al., 2013); Ghana	To ascertain early outcomes of the initial 20 consecutive localized PCa patients	Prospective cohort	RRP	20	5	19.5 (7-36).	NR	T1 (60.0) T2 (40.0)	16.12 (2.45-62.20)	NR	NR	62.7 (51-72)	IIEF > 16	Survival, Death, Peri/post-operative complications
(Rocha et al., 2022); Brazil	To report the intraoperative, functional, and oncological outcomes of patients who underwent RARP	Retrospective cohort	RARP	58	NR	40 (22-47)	NR	T1 (57.4) T2 (42.6)	5.87 (1.29-17.70)	6 (43.6) 7 (49.1) 8-9(7.3)	L (50.9) I (40.0) H (9.1)	62.5 (42-80)	Clavien-Dindo	BF, peri and Peri/post-operative complications
(Singh et al., 2020); India	To analyze the outcomes of localized PCa after RARP	Retrospective cohort	RARP	46	0	17 (1-60)	NR	T1 (86.9) T2 (13.0)	16.12 (2.45-62.20)	6 (41.3) 7 (6.5) 8 (2.2)	L (100.0)	60.8 ± 6.8	NA	BF
(Nazim et al., 2016); Pakistan	To describe the outcome of RRP for clinically localized PCa	Retrospective cohort	RRP	192	NR	41 (NR)	NR	T1 (27.0) T2 (72.0) T3 (1.0)	11±2.1 (1-121)	≤6 (50.0) 7 (37.3) ≥8 (3.7)	L (42.0) I (26.0) H (31.0)	63.6 ± 6 (43-77)	NR	Survival, BF, Death, Peri/post-operative complications
(Vorobev et al., 2021); Russia	To analyze the development of complications after RRP.	Prospective cohort	RRP	52	NR	48 (36-60)	NR	T1 (15.3) T2 (59.6) T3 (24.9)	NR	≤6 (48.0) 7 (34.6) ≥8 (17.3)	NR	64.2 ± 5.5	NR	Peri/post-operative complications

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Table 1 (*Continued*)

(Authors, Year); Country	Objective(s)	Study design	Treatment	Sample size	Hormonal therapy (%)	Follow-up mean/median (SD or range)	Period of toxicity (d)	T stage (%)	PSA mean/median (SD or range)	Gleason score (%)	Risk group (%)	Age mean/median (SD or range)	Tool	Extracted outcome
(Kim et al., 2012); Brazil	To report the cryoablation experience in the treatment of low and intermediate risk localized PCa	Case series	Cryotherapy	10	NR	13 (7-15)	Aute < 90	NR	7.8 ± 2.8	6 (60.0) 7 (40.0)	L (50.0) I (50.0)	66.2 ± 10.8	Clavien-Dindo	Erectile function status, urinary incontinence, BF, Peri/post-operative complications

Abbreviations: 2D = 2-dimensional radiation therapy; 3D-CRT = 3D-conformal radiation therapy; BCR = biochemical recurrence; bDFS = biochemical disease-free survival; BF = biochemical failure; BT = brachytherapy; CTCAE = common terminology criteria for adverse events version 4.0; DMFS = distant metastasis free survival; DSF = disease-free survival; EBRT = external beam radiation therapy; EORTC QLQ C30 = European organization for research and treatment of cancer quality of life questionnaire; EPIC = expanded prostate cancer index composite questionnaire; GI = gastrointestinal; GU = genitourinary; H = high risk group; HDR = high-dose-rate brachytherapy; I = intermediate risk group; IIEF-15/16 = international index of erectile function; IMRT = intensity modulated radiation therapy; IPSS = international prostate symptom score; L = low risk group; LDR = low-dose-rate brachytherapy; NA = not applicable; NCI CTC = National Cancer Institute Common Toxicity Criteria Version 4; NR = not reported; OS = overall survival; PCa = prostate cancer; PSA = prostate specific antigen; RARP = robotic-assisted radical prostatectomy; RP = radical prostatectomy; RRP = radical retropubic prostatectomy; RTOG = Radiation Therapy Oncology Group; SBRT = stereotactic body radiation therapy; T = clinical stage.

Late gastrointestinal toxicities

Four studies provided data on late gastrointestinal toxicity for patients who underwent 3D-CRT.[32,40,42,46] The pooled prevalence of late gastrointestinal grades 1-3 toxicities for patients that received 3D-CRT was 18% (95% [CI, 5%-32%]; I^2 = 95%, $P < .00001$), 3% (95% [CI, 0%-6%]; I^2 = 64%, $P = .04$), and 2% (95% [CI, 0%-3%]; I^2 = 0%, $P = .62$), respectively (see Table 2). It was not possible to perform a meta-analysis on the acute and late gastrointestinal toxicities for the single studies that evaluated 2D-RT,[32] IMRT,[30] and SBRT[43] (see Table 2).

Acute genitourinary toxicities

Three studies consisting of 246 patients who underwent 3D-CRT provided data on acute genitourinary toxicity.[32,42,46] The pooled prevalence of acute genitourinary grades 1-3 toxicities for patients that received 3D-CRT was 29% (95% [CI, 12%-47%]; I^2 = 91%, $P < .00001$), 16% (95% [CI, 1%-31%]; I^2 = 93%, $P < .00001$), and 3% (95% [CI, 0%-5%]; I^2 = 41%, $P = .18$), respectively (see Table 2).

Late genitourinary toxicities

Three studies consisting of 246 patients who underwent 3D-CRT provided data on late genitourinary toxicity.[32,42,46] The pooled prevalence of late genitourinary grades 1-3 toxicities for patients that received 3D-CRT was 13% (95% [CI, 1%-24%]; I^2 = 91%, $P < .00001$), 2% (95% [CI, 0%-3%]; I^2 = 0%, $P = .32$) and 2% (95% [CI, 0%-4%]; I^2 = 0%, $P = 1$), respectively (see Table 2). It was not possible to perform a meta-analysis on the acute and late genitourinary toxicity for the single studies that evaluated 2D-RT,[32] IMRT,[30] and SBRT.[43]

Acute skin toxicities

Two studies consisting of 135 patients who underwent 3D-CRT provided data on acute skin toxicity.[42,46] The pooled prevalence of acute skin grades 1-3 toxicities for patients that received 3D-CRT was 46% (95% [CI, 7%-85%]; I^2 = 96%, $P < .00001$), 14% (95% [CI, 0%-30%]; I^2 = 84%, $P = .01$), and 1% (95% [CI, 0%-3%]; I^2 = 0%, $P = .65$), respectively (see Fig. 3). It was not possible to perform a meta-analysis on the acute skin toxicity for the single study that evaluated 2D-RT.[32] The reported prevalence of acute skin grades 1-3 toxicities for the 2D-RT study group were 45% (95% CI, 35%-55%), 21% (95% CI, 13%-29%), and 10% (95% CI, 4%-16%), respectively.[32]

Late skin toxicities

Meta-analysis was not performed on late skin toxicity following EBRT because only one study provided information.[42] The grades 1 and 2 late skin toxicities after 3D-CRT were 64% (95% CI, 51%-77%) and 16% (95% CI, 5%-25%), respectively.

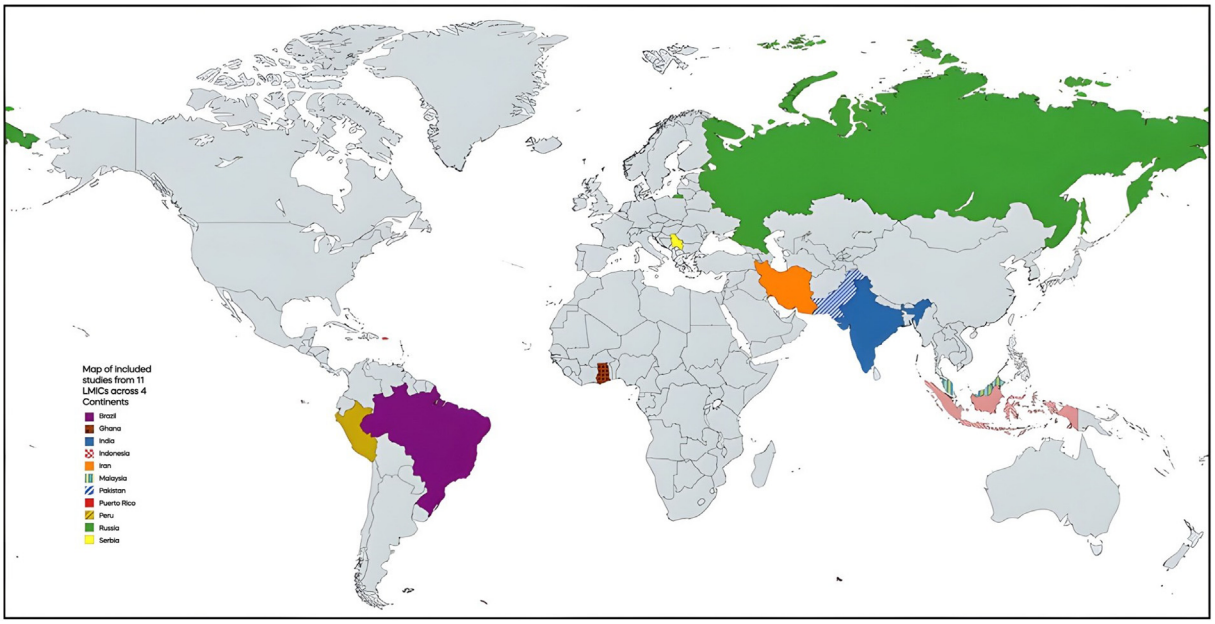

Figure 2 Geographic distribution of included studies.

Two-year biochemical failure

Two studies provided data on the 2-year biochemical failure of 271 participants who underwent 3D-CRT.[42,50] The pooled prevalence was 17% (95% [CI, 0%-47%]; $I^2 = 96\%$, $P < .00001$) (see Fig. 4). It was not possible to perform a meta-analysis on 3-year biochemical failure for the single study that evaluated SBRT[28] and 3D-CRT.[50] The prevalence of 3-year biochemical failure for patients who underwent SBRT and 3D-CRT was 3% (95% CI, 0%-9%) and 4% (95% CI, 0%-8%), respectively.

Five-year biochemical failure

Three studies consisting of 488 patients treated with EBRT provided data on biochemical failure.[32,37,50] The pooled prevalence of 5-year biochemical failure for patients that received 3D-CRT and 2D-RT were 18% (95% [CI, 0%-40%]; $I^2 = 97\%$, $P < .00001$) and 34% (95% [CI, 28%-41%]: $I^2 = 23\%$, $P = .25$), respectively (see Fig. 4).

Five-year overall survival

Three studies consisting of 289 patients who underwent 3D-CRT provided data on 5-year overall survival.[32,41,46] The pooled prevalence of 5-year overall survival following 3D-CRT was 87% (95% [CI, 84%-94%]; $I^2 = 88\%$, $P = .0002$) (see Fig. 5). However, it was not possible to perform meta-analysis on the single study that evaluated the 5-year overall survival following 2D-RT[32] and SBRT.[28]

Prostate cancer-specific death

The prevalence of prostate cancer-specific death following EBRT as reported by a single study was 13% (95% CI, 8%-18%).[32]

Cause of death other than prostate cancer

Two studies consisting of 285 patients who underwent EBRT provided data on the cause of death other than prostate cancer.[32,46] The pooled prevalence of mortality other than prostate cancer was 7% (95% [CI, 3%-11%]; $I^2 = 42\%$, $P = .19$) (see Fig. 6).

Outcomes and toxicities following brachytherapy

Acute gastrointestinal toxicities

The acute gastrointestinal grades 1 and 2 toxicities of 90 patients treated with brachytherapy alone as reported by a single study were 25% (95% CI, 16%-24%) and 1% (95% CI, 0%-3%), respectively[34] (see Table 2).

Late gastrointestinal toxicities

Two studies consisting of 180 patients who underwent brachytherapy alone provided data on late gastrointestinal toxicities.[34,48] However, meta-analysis could not be performed because different toxicity assessment tools were used in each study. The late gastrointestinal grades 1-3 toxicities assessed with RTOG after brachytherapy were 1% (95% CI, 0%-3%), 6% (95% CI, 1%-11%), and 2% (95% CI, 0%-5%), respectively[34] (see Table 2). The late gastrointestinal grades 1 and 2 toxicities assessed with CTCAE after brachytherapy were 3% (95% CI, 0%-7%) and 1% (95% CI, 0%-3%), respectively.[48]

Acute genitourinary toxicities. Two studies consisting of 281 patients who underwent brachytherapy provided data on acute genitourinary grade 1 toxicity using CTCAE

Table 2 Prevalence of gastrointestinal and genitourinary toxicities following prostate cancer radiation treatment assessed with RTOG

Technique	Number of studies	Sample size	Prevalence of acute gastrointestinal toxicities % (95% CI)				Prevalence of late gastrointestinal toxicities % (95% CI)				Prevalence of acute genitourinary toxicities % (95% CI)				Prevalence of late genitourinary toxicities % (95% CI)			
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
3D-CRT*	4	340	24 (8-41)	17 (3-31)	1 (0-3)	NR	18 (5-32)	3 (0-6)	2 (0-3)	NR	NR	NR	NR	NR	NR	NR	NR	NR
3D-CRT*	3	340	NR	NR	NR	NR	NR	NR	NR	NR	29 (12-47)	16 (1-31)	3 (0-5)	NR	13 (1-24)	2 (0-3)	2 (0-4)	NR
2D-RT	1	92	16 (9-23)	13 (6-20)	3 (0-7)	NR	11 (5-17)	6 (1-11)	3 (0-7)	NR	23 (14-32)	7 (2-12)	5 (0-10)	NR	1 (0-3)	4 (0-8)	5 (0-10)	NR
IMRT	1	40	48 (33-63)	13 (3-23)	NR	NR	NR	NR	NR	NR	65 (50-80)	1 (0-10)	NR	NR	NR	NR	NR	NR
SBRT	1	49	14 (4-24)	NR	NR	NR	6 (0-13)	NR	2 (0-6)	NR	45 (31-59)	NR	2 (0-6)	NR	6 (0-13)	NR	2 (0-6)	NR
BT	1	90	25 (16-24)	1 (0-3)	NR	NR	1 (0-3)	6 (1-11)	2 (0-5)	NR	58 (48-68)	10 (14-16)	7 (2-12)	5(0-10)	13 (6-20)	3 (0-7)	3 (0-7)	2 (0-5)
BT+EBRT	1	39	NR	NR	NR	NR	NR	NR	NR	NR	15 (4-22)	18 (6-30)	5 (0-12)	NR	15 (4-22)	5 (0-12)	3 (0-8)	NR

Abbreviations: 2D-RT = 2-dimensional radiation therapy; 3D-CRT = 3D-conformal radiation therapy; BT = brachytherapy; EBRT = external beam radiation therapy; IMRT = intensity modulated radiation therapy; NR = not reported; SBRT = stereotactic body radiation therapy.
*Summary of pooled estimators obtained with meta-analyses; forest plot shown in Appendix E3.

as the assessment tool.[31,48] The pooled prevalence of acute genitourinary grade 1 toxicity for patients who received brachytherapy was 19% (95% [CI, 0%-50%]; I^2 = 96%, P < .00001) (see Fig. 7). It was not possible to perform a meta-analysis for studies that evaluated acute genitourinary toxicities after brachytherapy using different assessment tools.[31,34] The acute genitourinary grades 1-4 toxicities assessed with RTOG after brachytherapy were 58% (95% CI, 48%-68%), 10% (95% CI, 14%-16%), 7% (95% CI, 2%-12%), and 5% (95% CI, 0%-10%), respectively[34] (see Table 2). The acute genitourinary grades 2, and 3 toxicities assessed with CTCAE after brachytherapy were 11% (95% CI, 6%-16%) and 2% (95% CI, 0%-4%), respectively.[31]

Late genitourinary toxicities

Two studies consisting of 281 patients who underwent brachytherapy provided data on late genitourinary toxicities.[34,48] However, a meta-analysis could not be performed because different toxicity assessment tools were used. The late genitourinary grades 1-4 toxicities assessed with RTOG after brachytherapy were 13% (95% CI, 6%-20%), 3% (95% CI, 0%-7%), 3% (95% CI, 0%-7%), and 2% (95% CI, 0%-5%), respectively[34] (see Table 2). The late genitourinary grades 1-3 toxicities assessed with CTCAE after brachytherapy were 12% (95% CI, 7%-17%), 3% (95% CI, 1%-5%), and 1% (95% CI, 0%-2%), respectively.[31]

Three-year biochemical failure

The prevalence of the 3-year biochemical failure as reported by a single study following brachytherapy was 4% (95% CI, 1%-7%).[31]

Five-year biochemical failure

Three studies comprising 244 patients who underwent brachytherapy alone provided information for biochemical failure analysis.[33,34,48] The pooled prevalence for the 5-year biochemical failure following brachytherapy was 30% (95% [CI, 3%-58%]; I^2 = 97%, P < .00001) (see Fig. 4).

Prostate cancer-specific death

The prevalence of prostate cancer-specific death following brachytherapy as reported by a single study was 1% (95% CI, 0%-3%).[48]

Outcomes and toxicities following combined brachytherapy and EBRT

Gastrointestinal toxicities

The prevalence of grades 1-4 gastrointestinal toxicities as reported by a single study of 130 patients following combined brachytherapy and EBRT were 26% (95% CI, 19%-33%), 40% (95% CI, 32%-48%), 20%

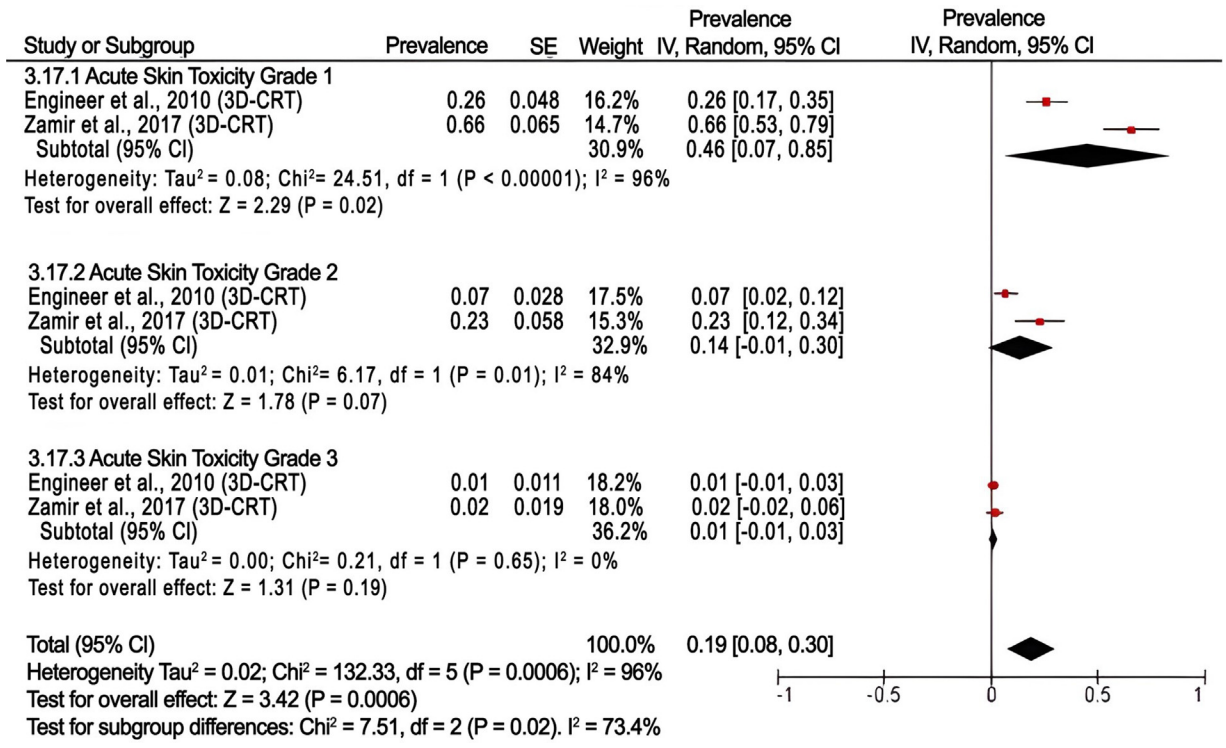

Figure 3 Forest plot for the prevalence of acute skin toxicity after 3-dimensional conformal radiation therapy.

(95% CI, 13%-27%), and 14% (95% CI, 8%-20%), respectively.[35] The toxicity was not categorized whether acute or late; however, assessment was done using CTCv5.

Genitourinary toxicities

The prevalence of grades 1-4 acute genitourinary toxicities as reported by a single study of 130 patients following combined brachytherapy and EBRT were 19% (95% CI, 12% -26%), 41% (95% CI, 33%-49%), 34% (95% CI, 26%-42%), and 6% (95% CI, 2%-10%), respectively.[35] The toxicity was not categorized whether acute or late however assessment was done using CTCv5.

Acute genitourinary toxicities

The prevalence of grades 1-3 acute genitourinary toxicities following combined brachytherapy and EBRT in 39 patients were 15% (95% CI, 4% -26%), 18% (95% CI, 6%-30%), and 5% (95% CI, 0%-12%), respectively[29] (see Table 2).

Late genitourinary toxicities

The prevalence of grades 1-3 late genitourinary toxicities following combined brachytherapy and EBRT of 39 patients were 15% (95% CI, 4% -26%), 5% (95% CI, 0%-12%), and 3% (95% CI, 0%-8%), respectively[29] (see Table 2).

Three-year biochemical failure

Three studies provided data on biochemical failure following combined brachytherapy and EBRT.[29,35,36] The pooled prevalence of 3-year biochemical failure following combined brachytherapy and EBRT was 16% (95% [CI, 4%-27%]; $I^2 = 87\%$, $P = .0004$) (see Fig. 4).

Five-year overall survival

Two studies consisting of 248 patients who underwent combined treatment of brachytherapy and EBRT provided data on 5-year overall survival.[29,36] The pooled prevalence of 5-year overall survival was 96% (95% [CI, 93%-98%]; $I^2 = 0\%$, $P = .38$) (see Fig. 5).

Prostate cancer-specific death

The prevalence of prostate cancer-specific death following combined brachytherapy and EBRT as reported by a single study was 2% (95% CI, 0%-4%).[36]

Cause of death other than prostate cancer

Two studies consisting of 299 patients who underwent combined treatment of EBRT and brachytherapy provided data on causes of death other than prostate cancer.[34,36] The pooled prevalence of mortality other than prostate cancer was 7% (95% [CI, 2%-17%]; $I^2 = 86\%$, $P = .007$) (see Fig. 6).

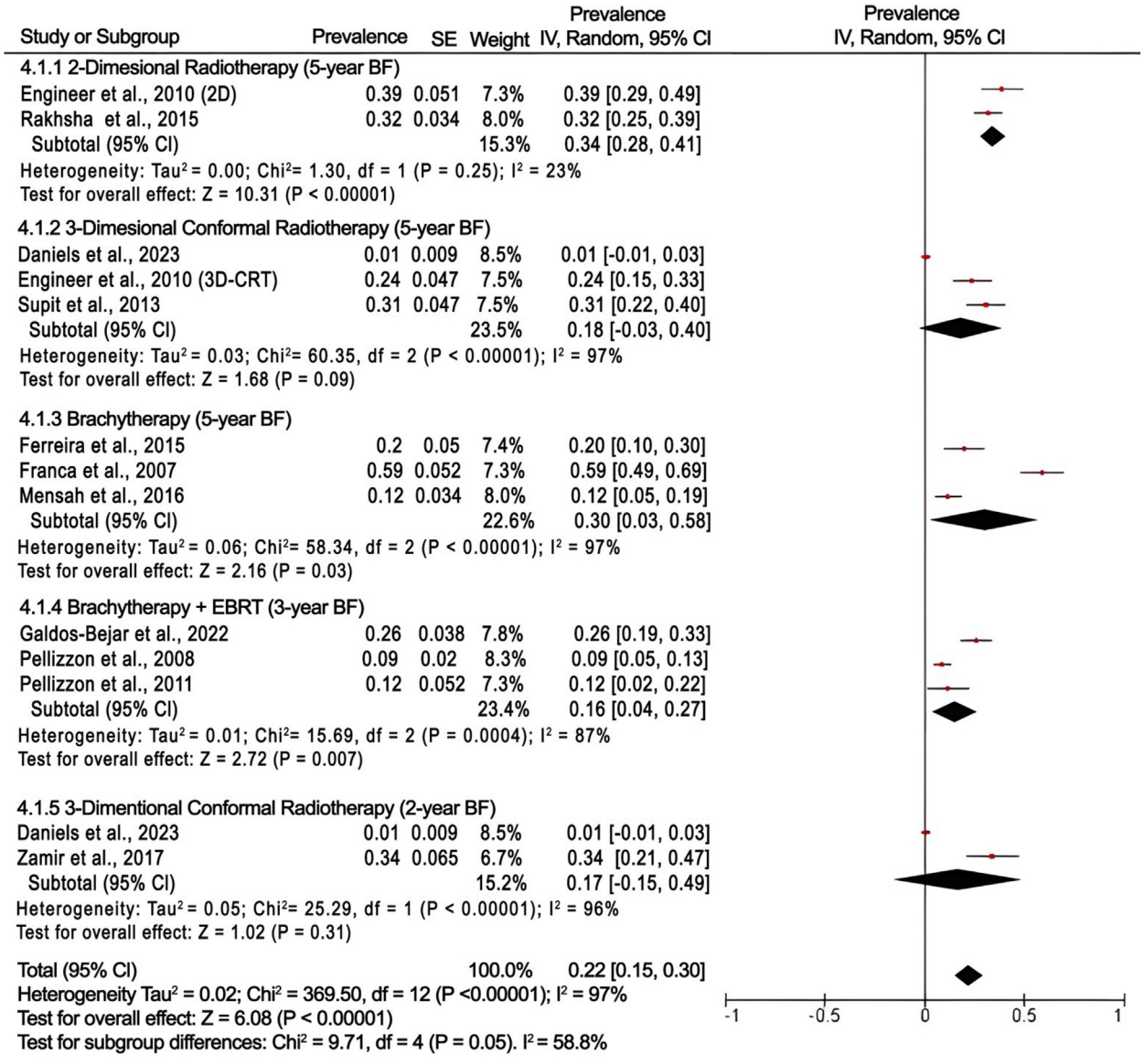

Figure 4 Forest plot for the prevalence of biochemical failure following radiation therapy.

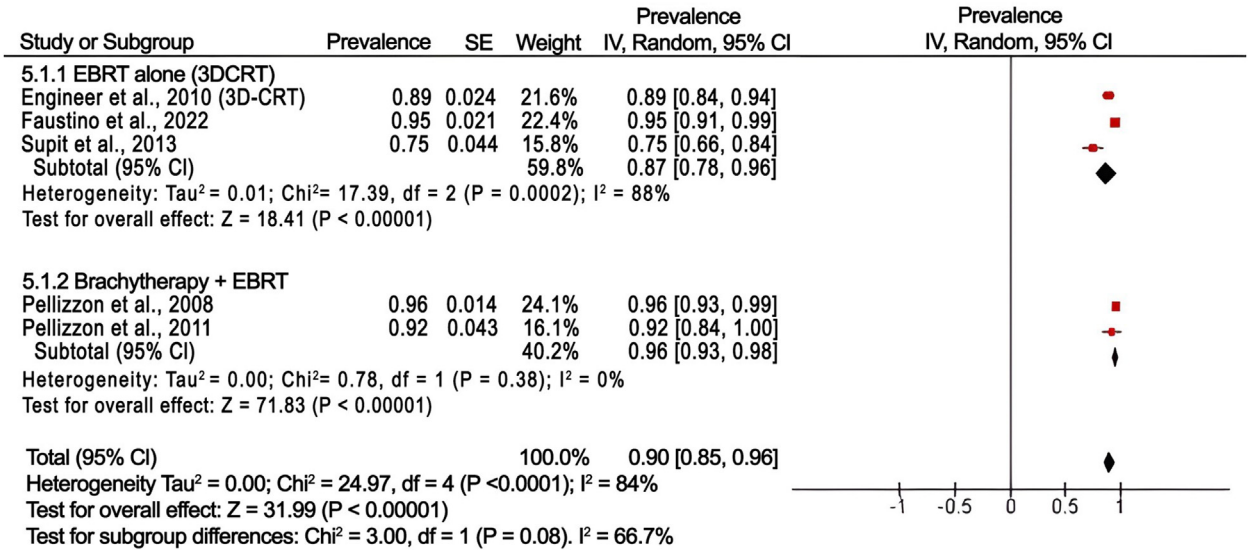

Figure 5 Forest plot for the prevalence of 5-year overall survival following radiation therapy.

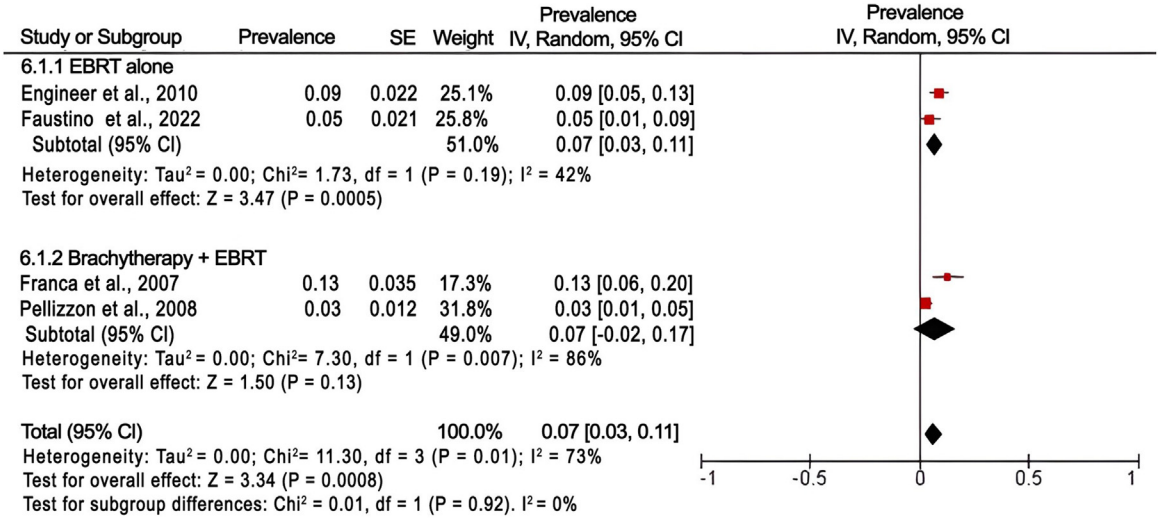

Figure 6 Forest plot for the prevalence of cause of death other than prostate cancer following radiation therapy.

Outcomes and toxicities following radical prostatectomy

Gastrointestinal toxicities

Only one study comprising 419 patients treated with RRP evaluated gastrointestinal toxicities.[35] The prevalence of grades 1-4 gastrointestinal toxicities following RRP was 31% (95% CI, 26%-36%), 29% (95% CI, 25%-33%), 23% (95% CI, 28%-38%), and 6% (95% CI, 4%-8%), respectively. The toxicity was not categorized whether acute or late; however, assessment was done using CTCv5.

Genitourinary toxicities

Only one study comprising 419 patients treated with RRP evaluated genitourinary toxicities.[35] The prevalence

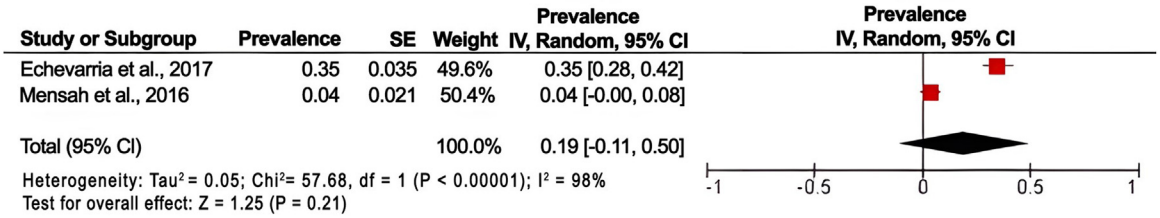

Figure 7 Forest plot for prevalence of acute genitourinary toxicity following brachytherapy.

of grades 1-4 genitourinary toxicities following RRP was 23% (95% CI, 19% -27%), 52% (95% CI, 44%-60%), 21% (95% CI, 17%-25%), and 4% (95% CI, 2%-6%), respectively. The toxicity was not categorized whether acute or late; however, assessment was done using CTCv5.

Perioperative rectal injury

Two studies with 242 patients treated with RRP provided data on perioperative rectal injury.[47] The prevalence of perioperative rectal injury among patients who received RRP was 2% (95% [CI, 0%-5%]; I^2 = 37%, P = .21) (see Appendix E4).

Positive surgical margins

Two studies consisting of 242 patients who underwent RRP provided data on positive surgical margins.[44,47] The pooled prevalence of positive surgical margins for patients that received RRP was 13% (95% [CI, 9%-18%]; I^2 = 0%, P = .72) (see Appendix E4).

Postoperative urethral stricture

Two studies consisting of 244 patients who underwent RRP provided data on postoperative urethral stricture.[44,49] The pooled prevalence of postoperative urethral stricture for patients who received RRP was 8% (95% [CI, 5%-12%]; I^2 = 0%, $P < .67$) (see Appendix E4).

Four-year biochemical failure

Two studies consisting of 611 patients who were treated with radical prostatectomy provided data on 4-year biochemical failure.[35,44] The pooled prevalence of the 4-year biochemical failure following RRP was 22% (95% [CI, 0%-51%]; I^2 = 99%, P = .0004) (see Appendix E4).

Postoperative complications following cryotherapy

Only one study with 10 patients treated with cryotherapy provided evidence of postoperative complications.[51] The study used the Clavein-Dindo Classification for the assessment of complications. The prevalence of Clavein-Dindo grade 1 complications of patients treated with cryotherapy included: dysuria 10% (95% CI, 0%-29%); hematuria 30% (95% CI, 25%-35%); perineal pain 10% (95% CI, 0%-29%); scrotal hematoma 10% (95% CI, 0%-29%); and urinary retention 20% (95% CI, 0%-45%).[51]

Discussion

Evidence on treatment-related outcomes and toxicities is essential particularly to support clinical decision-making given the plethora of treatments available for the management of cancer. In less-resourced countries such as LMICs, such information is crucial to support policymakers in channeling resources to areas where assistance are needed the most. This systematic review and meta-analysis therefore sought to report the prevalence of treatment-related outcomes and toxicities among men diagnosed with localized prostate cancer in LMICs.

Based on the pooled results, localized prostate cancer in LMICs is managed with EBRT, radical prostatectomy, and brachytherapy, either alone or combined. All treatment regimens included androgen deprivation therapy except for a few that did not report. Of the radiation therapy option, 3D-CRT was commonly used indicating the transition from 2D Cobalt 60 treatment. Patients treated with surgery underwent mostly RRP. Only one study reported on focal therapy (cryotherapy) indicating low uptake of this modality. Advanced therapy such as IMRT, SBRT, VMAT, high dose-rate brachytherapy, and robot-assisted radical prostatectomy were limited. Notwithstanding, basic localized prostate cancer treatment has always been difficult to access in LMICs, be it surgery, or radiation therapy because of cost, limited facilities, lack of skilled personnel, and political instability. This systematic review is therefore limited in reporting outcomes of poor patients resorting to unconventional treatment regimens. The most prevalent clinician-reported toxicities following radiation therapy were acute skin grade 1, acute genitourinary grade 1, acute gastrointestinal grade 1, and late gastrointestinal grade 1, with less prevalence of grade $\geq$ 2. Perioperative rectal injury was the least prevalent toxicity after RRP. The 5-year survival rate following 3D-CRT was 87%, which increased to 96% for the combined brachytherapy and EBRT group.

The pooled prevalence of severe clinician-reported genitourinary and gastrointestinal toxicities was generally low; however, there were some disparities. It is well established that 3D-CRT offers more conformity against 2D; in this review, the prevalence of severe toxicities was high among those treated with 2D. However, compared with an Italian study,[52] prevalence of severe genitourinary and gastrointestinal toxicity both acute and late grade $\geq$ 2 following 3D-CRT were lower than what was found in this review. While their study was underpowered, the use of image-guided cone beam computerized verification which allows for more precise dose delivery to the target thereby sparing most of the organ at risk[53] might have influenced their result. Evidence of a more recent publication of a 10-year follow up from the same country showed slightly high severe late toxicities,[54] which might be because of the long follow up time allowing for more late effects to be recorded.

Advances in technology and imaging are considerably changing prostate cancer treatment, IMRT is currently the standard of care in HICs with SBRT and VMAT being used effectively. These techniques allow for dose escalation while achieving safe dose-volume constraints for organs at risk. The advantages of these techniques are

well established.[55-57] These sophisticated treatments are emerging in LMICs. In this review, while grade 2 and worst toxicities were low or not experienced for IMRT and SBRT, the prevalence of acute grade 1 genitourinary was quite high. For efficient and safe use of these technologies, LMICs should be equipped with infrastructure, trained staff, funding, robust quality assurance program, and strategic framework for integrating these advanced technologies into existing systems.

The results of the meta-analysis indicated that oncological outcomes for men with localized prostate cancer in LMICs were satisfactory however differences in follow-up timing makes it challenging to compare across treatments. The 5-year biochemical failure following combined treatment of brachytherapy and EBRT was low compared to the individual treatments, this is consistent with a recent systematic review which found combined brachytherapy and EBRT to be superior.[14] Similarly, the 5-year survival rate favored combined brachytherapy and EBRT as against EBRT alone. The possibility of dose escalation with the combined technique might have been an advantage. The 4-year biochemical failure after radical prostatectomy was slightly lower than that reported by Daskivich et al[58] at 5 years. The difference might be because of the timing of biochemical failure. More long-term follow up studies are needed to provide meaningful evidence.

This systematic review and meta-analysis is the first to provide pooled evidence on treatment-related outcomes and toxicities for localized prostate cancer in LMICs. The comprehensive search strategies, rigorous selection criteria, and a thorough review process enhance the strength of this study. However, the search strategy was restricted to English publications; hence, it is likely some eligible articles might have been missed. It was not possible to perform a meta-analysis on emerging treatments, some endpoints, and risk profiling because of limited studies and the usage of variable assessment tools. The result may be skewed to middle-income countries as publication from low-income countries was limited.

Conclusions

The systematic review and meta-analysis indicated that treatment for localized prostate cancer in LMICs has a favorable toxicity profile and oncological outcomes. Acute and late genitourinary and gastrointestinal toxicities were well tolerated following localized prostate cancer treatment. Rates of biochemical failure and overall survival were satisfactory. However, early detection, treatment accessibility, regular post-treatment follow-ups and care, consistent quality assurance practices, and staff continues development could help minimize treatment toxicities and improve outcomes of localized prostate cancer in LMICs.

Disclosures

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101670.

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