Systematic review and/or Meta-analysis

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Robotic-assisted versus laparoscopic radical prostatectomy for prostate cancer: the first separate systematic review and meta-analysis of randomised controlled trials and non-randomised studies

Jianglei Ma, MBBS[a], Weidong Xu, MSc[a], Rui Chen, MD[b], Yasheng Zhu, MD[a], Ye Wang, MSc[b], Wanli Cao, MD[a], Guanqun Ju, MD[a], Jizhong Ren, PhD, MD[a], Xiaofei Ye, PhD[c], Qian He, PhD[c], Yifan Chang, MD[b,*], Shancheng Ren, PhD, MD[a,*]

Background: Due to the lack of sufficient evidence, it is not clear whether robotic-assisted radical prostatectomy (RARP) or laparoscopic radical prostatectomy (LRP) is better for prostate cancer. The authors conducted this study by separately pooling and analysing randomised controlled trials (RCTs) and non-randomised studies to compare the perioperative, functional, and oncologic outcomes between RARP and LRP.

Methods: A systematic literature search was performed in March 2022 using Cochrane Library, Pubmed, Embase, Medline, Web of Science, and China National Knowledge Infrastructure. Two independent reviewers performed literature screening, data extraction and quality assessment according to the Preferred Reporting Items for Systematic Review and Meta-analysis statement. Subgroup analysis and sensitivity analysis were performed.

Results: A total of 46 articles were included, including 4 from 3 RCTs and 42 from non-randomised studies. For RCTs, meta-analysis showed that RARP and LRP were similar in blood loss, catheter indwelling time, overall complication rate, overall positive surgical margin and biochemical recurrence rates, but quantitative synthesis of non-randomised studies showed that RARP was associated with less blood loss [weighted mean difference (WMD) = −71.99, 95% CI −99.37 to −44.61, $P < 0.001$], shorter catheterization duration (WMD = −1.03, 95% CI −1.84 to −0.22, $P = 0.010$), shorter hospital stay (WMD = −0.41, 95% CI −0.68 to −0.13, $P = 0.004$), lower transfusion rate (OR = 0.44, 95% CI 0.35–0.56, $P < 0.001$), lower overall complication rate (OR = 0.72, 95% CI 0.54–0.96, $P = 0.020$), and lower biochemical recurrence rate (OR = 0.78, 95% CI 0.66–0.92, $P = 0.004$), compared with LRP. Both meta-analysis of RCTs and quantitative synthesis of non-randomised studies showed that RARP was associated with improved functional outcomes. From the results of the meta-analysis of RCTs, RARP was higher than LRP in terms of overall continence recovery [odds ratio (OR) = 1.60, 95% CI 1.16–2.20, $P = 0.004$), overall erectile function recovery (OR = 4.07, 95% CI 2.51–6.60, $P < 0.001$), continence recovery at 1 month (OR = 2.14, 95% CI 1.25–3.66, $P = 0.005$), 3 (OR = 1.51, 95% CI 1.12–2.02, $P = 0.006$), 6 (OR = 2.66, 95% CI 1.31–5.40, $P = 0.007$), and 12 months (OR = 3.52, 95% CI 1.36–9.13, $P = 0.010$) postoperatively, and potency recovery at 3 (OR = 4.25, 95% CI 1.67–10.82, $P = 0.002$), 6 (OR = 3.52, 95% CI 1.31–9.44, $P = 0.010$), and 12 months (OR = 3.59, 95% CI 1.78–7.27, $P < 0.001$) postoperatively, which were consistent with the quantitative synthesis of non-randomised studies. When sensitivity analysis was performed, the results remained largely unchanged, but the heterogeneity among studies was greatly reduced.

Conclusion: This study suggests that RARP can improve functional outcomes compared with LRP. Meanwhile, RARP has potential advantages in perioperative and oncologic outcomes.

Keywords: laparoscopic, meta-analysis, prostate cancer, radical prostatectomy, robotic

[a]Department of Urology, Changzheng Hospital, [b]Department of Urology, Changhai Hospital and [c]Department of Health Statistics, Naval Medical University, Shanghai, China

J.M., W.X. and R.C. contributed equally to this study

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**Corresponding author. Address: Changhai Road 168, Yangpu District, Shanghai 200433, China; Fengyang Road 415, Huangpu District, Shanghai 200003, China. Tel.: +86-13661-652533; +86-13917-793885, fax: +86-21-3116-1718. E-mail address: 13661652533@163.com (Y. Chang); E-mail address: renshancheng@gmail.com (S. Ren).*

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Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the fifth leading cause of cancer death in men around the world, accounting for 14.1% of total new cancer cases and 6.8% of total cancer deaths in men in 2020[1]. Radical prostatectomy (RP) is the only surgical option for patients with resectable PCa, and the only treatment for resectable PCa to show a benefit for overall survival[2,3]. Open radical prostatectomy has been the standard in the treatment of PCa for some time; however, it is associated with complications and sequela, including considerable blood loss, postoperative urinary incontinence, and erectile dysfunction.

In order to reduce the damage of traditional open surgery and improve functional outcomes, laparoscopic radical prostatectomy (LRP) has been rapidly developed and emerged as an alternative to open radical prostatectomy since LRP was first reported in the early 1990s[4–7]. In recent years, LRP has been recognised for its advantages of minimally invasive surgery in the treatment of PCa, such as reduced blood loss, shorter hospital stay, and lower rates of urinary incontinence and erectile dysfunction, compared with open surgery[8–10]. However, conventional laparoscopic surgery has also limitations of itself, including decreased sense of touch, two-dimensional images, and amplification of hand tremor. Besides, LRP requires a steep learning curve for surgeons[11].

Subsequently, robotic-assisted radical prostatectomy (RARP), an excellent evolution of minimally invasive surgery providing three-dimensional (3D) images and flexible robotic arms to reduce the difficulties of complex laparoscopic procedures, has been widely adopted in the treatment of PCa since 2001[12–16]. However, due to the lack of high-level evidence, the controversy still exists as to whether the above-mentioned advantages of RARP over LRP are more advantageous in functional protection and cancer control for PCa patients. So far, only three randomised controlled trials (RCTs) have investigated the differences between RARP and conventional LRP for PCa[17–19]. However, the limitations of these trials are single-surgeon settings and short-term study periods, which are far from reaching a convincing conclusion. Therefore, we conducted this systematic review and meta-analysis of RCTs and non-randomised studies to explore and evaluate the perioperative, functional, and oncologic outcomes between LRP and RARP.

HIGHLIGHTS

- This is the first systematic review and meta-analysis to report separate summary estimates for randomised controlled trials and non-randomised studies separately.
- This is the largest meta-analysis to date comparing robotic-assisted radical prostatectomy with laparoscopic radical prostatectomy for prostate cancer.
- Both meta-analysis of randomised controlled trials and meta-analysis of non-randomised studies found that robot-assisted radical prostatectomy could better promote postoperative functional recovery.
- The meta-analysis of non-randomised studies found that robotic surgery also had potential advantages in improving perioperative and oncological outcomes of patients with prostate cancer.

Methods

This systematic review and meta-analysis was registered with PROSPERO on 16 May 2022 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022330470). This study was strictly conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and the PRISMA checklist was completed[20], Supplemental Digital Content 1, http://links.lww.com/JS9/A364. Methodological assessment using the AMSTAR 2 checklist showed a high-quality review[21], Supplemental Digital Content 2, http://links.lww.com/JS9/A365.

Search strategy

We performed a systematic literature search in Cochrane Library, Pubmed, Embase, Medline, Web of Science, and China National Knowledge Infrastructure for articles published before March 2022 that evaluated the comparison between RARP and LRP in the treatment of PCa. Search strategies in detail are provided in the Supplement, Supplemental Digital Content 3, http://links.lww.com/JS9/A366. Additionally, the reference lists of all relevant articles were also searched to find the additional literature. Two reviewers independently screened each record and each report retrieved.

Inclusion criteria and exclusion criteria

The inclusion criteria were as follows: (1) Clinical studies comparing RARP with LRP for patients with PCa; (2) Full-text articles that reported at least one of outcomes which interest us; (3) For multiple studies with duplicate cases reported by the same teams or institutions, only the most recent or largest study was included. However, the earlier or smaller ones could be used to analyse outcomes not reported by the former. If two or more studies included totally different cases from the same institutions, we would still analyse the data from these studies.

The exclusion criteria were as follows: (1) Case reports, reviews, letters, meeting abstracts, editorial comments, and other non-related studies; (2) Studies without necessary data for statistical analysis, such as those that lacked means or standard deviations; (3) Studies that were not comparative.

Data extraction and quality assessment of included studies

Two reviewers individually extracted the data from all included researches. The controversial results were settled by discussion, and a final decision was made by a third investigator. We recorded the following data: (1) Baseline data: first author, year of publication, country, study design, and sample size; (2) Characteristics of participants: age, BMI, preoperative prostate-specific antigen (PSA); (3) Perioperative outcomes: operative time, estimated blood loss, transfusion rate, catheterization duration, hospital stay, and overall complication rates; (4) Functional outcomes: overall continence and erectile function recovery rate, and follow-up data at different time points; (5) Oncologic outcomes: positive surgical margin (PSM) and biochemical recurrence (BCR) rates. If the study reported the median, range, and inter-quartile range, the mean and SD were calculated according to the methods described by Luo *et al.*[22] and Wan *et al.*[23], respectively.

For the RCTs, the Cochrane Collaboration's risk of bias tool was used to conduct the quality evaluation. The quality of non-randomised studies was evaluated using the Newcastle–Ottawa Scale (NOS)[24]. The NOS scores were assessed using a nine-point system. Studies with NOS scores of 7–9, 4–6, and 1–3 were judged to be of high, moderate, and low quality, respectively[25]. Only high-quality studies were included in the meta-analysis.

Subgroup and sensitivity analysis

As far as we know, because the number of published RCTs was too small to allow subgroup analysis, we would perform subgroup analyses in non-randomised studies. To reduce selection bias of included patients, we would group studies according to whether or not propensity score matched analysis (PSMA) was performed. PSMA was defined as matching analysis based on baseline characteristics of included patients (e.g. age and BMI, etc.) to reduce the effect of confounding variables on the results. We would perform a sensitivity analysis by excluding literature to verify the robustness of the overall effect size.

Statistical analysis

Considering the inherent differences between RCTs and non-randomised studies, if they were combined for meta-analysis, the accuracy of the results might be affected. Therefore, we would perform a separate pooled analysis of the included RCTs and non-randomised studies[26]. Statistical analyses were conducted using the Review Manager 5.4 software (Cochrane Collaboration). For continuous variables, the results were represented as weighted mean difference (WMD) with a 95% CI, and for dichotomous variables expressed as odds ratio (OR) with a 95% CI. The I^2 statistic with a cut-off of $> 56\%$ and the χ^2 test were used to assess and define the significant heterogeneity[27]. If the heterogeneity was high, a random effect model was adopted. Otherwise, we used a fixed-effect model. Meta-analyses of continuous variables were performed using the Inverse Variance method, and dichotomous variables were pooled using the Mantel–Haenszel method. The potential publication bias was evaluated by visually inspecting the funnel plots. P less than 0.05 was regarded as statistically significant.

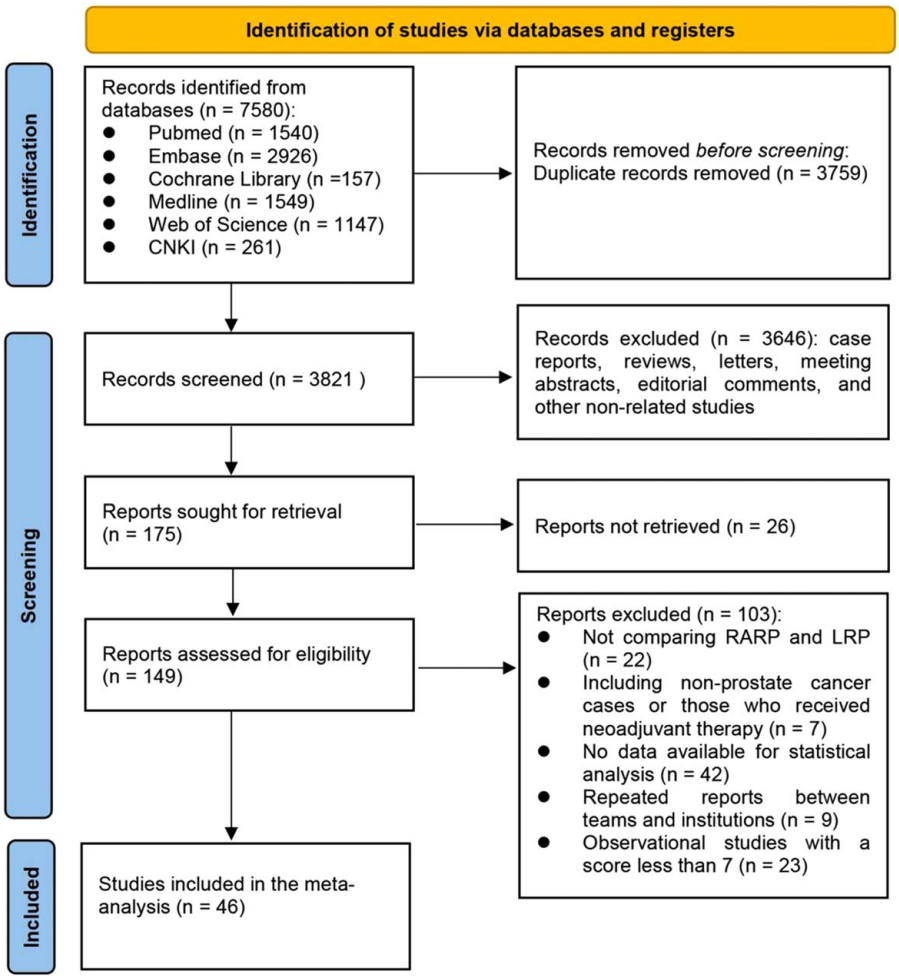

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis flow chart of literature search strategies. LRP, laparoscopic radical prostatectomy; RARP, robotic-assisted radical prostatectomy.

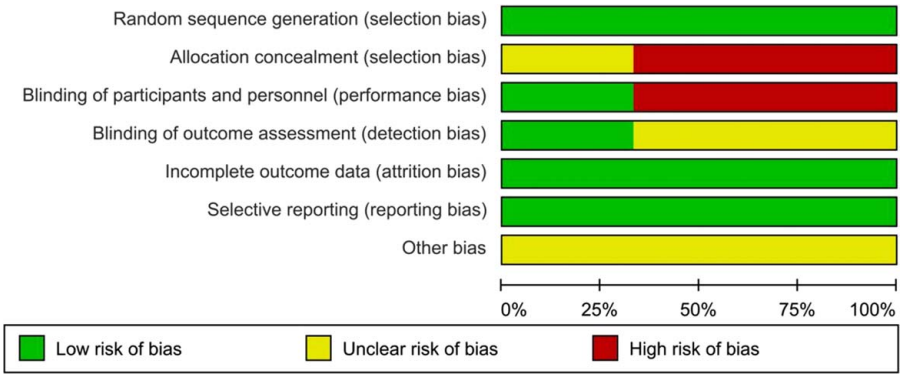

Figure 2. Risk of bias graph of included randomised controlled trials.

Results

Selected studies and characteristics of studies

A total of 46 articles with 16 700 patients, of whom 10 061 patients were in the RARP group and 6639 in the LRP group, were involved in the analysis[17–19,28–70]. The flow chart of the screening strategies, which contains reasons for the exclusion of studies, is illustrated in Figure 1. Forty-two included studies were published in English[17–19,28–32,35–56,58–63,65–70], two in Chinese[33,34,] and two in French[57,64]. Of the 46 articles, four were from three RCTs and 42 were from non-randomised studies. Eight of the non-randomised studies were prospective and 34 were retrospective. The basic characteristics of the included studies are listed in Table S1, Supplemental Digital Content 3, http://links.lww.com/JS9/A366.

The bias risk assessment results of three RCTs are shown in Figure 2 and Figure S3. All RCTs were found to be low risk of bias for random sequence generation, incomplete outcome data and selective reporting. There was an unclear or high risk of bias relating to allocation concealment and blinding of outcome assessments. The quality assessment of the included non-randomised studies according to the NOS is elucidated in Table S2, Supplemental Digital Content 3, http://links.lww.com/JS9/A366. It showed that 12 of the 42 included studies had seven stars[35,37,39,44,49,53,57,59,60,63,67,68], 20 had eight stars[30,32–34,40–43,46,48,50–52,54,61,62,64,66,69,70], and 10 had nine stars[29,31,36,38,45,47,55,56,58,65].

Perioperative outcomes

All results of meta-analysis of RCTs and quantitative synthesis of non-randomised studies are summarised in Table 1. From the results of the pooled analysis of RCTs, RARP was associated with longer operative time compared with LRP (WMD = 5.64, 95% CI 0.34–10.94, $P = 0.040$, $I^2 = 0\%$). No statistically significant differences were found in terms of blood loss (WMD = 2.95, 95% CI – 56.84 to 62.74, $P = 0.920$, $I^2 = 80\%$) and duration of catheterization (WMD = – 0.34, 95% CI – 1.31 to 0.64, $P = 0.500$, $I^2 = 77\%$), but the statistical heterogeneity was high. All RCTs including a total of 993 patients reported the overall complication rates. There were no statistically significant differences between the two groups regarding overall complication rates (OR = 0.87, 95% CI 0.60–1.25, $P = 0.440$, $I^2 = 50\%$). (Fig. S1–S4, Supplemental Digital Content 3, http://links.lww.com/JS9/A366).

From the results of the quantitative synthesis of non-randomised studies, compared with LRP, RARP was associated with less blood loss (WMD = – 71.99, 95% CI – 99.37 to – 44.61, $P < 0.001$, $I^2 = 91\%$), shorter catheterization duration (WMD = – 1.03, 95% CI – 1.84 to – 0.22, $P = 0.010$, $I^2 = 92\%$), shorter hospital stay (WMD = – 0.41, 95% CI – 0.68 to – 0.13, $P = 0.004$, $I^2 = 87\%$), and lower overall complication rates (OR = 0.72, 95% CI 0.54–0.96, $P = 0.020$, $I^2 = 54\%$). In terms of transfusion rate, the results of the quantitative synthesis of 17 non-randomised studies revealed that transfusion rate was lower in RARP than LRP (OR = 0.44, 95% CI 0.35–0.56, $P < 0.001$, $I^2 = 32\%$). Twenty four studies reported the operative time. The pooled data based on 24 studies revealed no significant difference between the groups of RARP and LRP (WMD = 3.00, 95% CI – 14.05 to 20.05, $P = 0.730$, $I^2 = 98\%$). (Fig. S19–S24, Supplemental Digital Content 3, http://links.lww.com/JS9/A366)

Functional outcomes

In terms of overall urinary continence recovery rate, the meta-analysis of RCTs showed a statistically significant advantage in favour of RARP (OR = 1.60, 95% CI 1.16–2.20, $P = 0.004$). Furthermore, RARP was associated with obviously improved outcomes for urinary continence rate to those of LRP at 1 (OR = 2.14, 95% CI 1.25–3.66, $P = 0.005$), 3 (OR = 1.51, 95% CI 1.12–2.02, $P = 0.006$), 6 (OR = 2.66, 95% CI 1.31–5.40, $P = 0.007$), and 12 months (OR = 3.52, 95% CI 1.36–9.13, $P = 0.010$) after surgery. Based on the results of the pooled analysis of three RCTs, the overall potency recovery rate was 25.8% (58 of 225 cases) after LRP, while it was found to be 33.6% (144 of 428 cases) after RARP. Certainly, the meta-analysis demonstrated that patients with RARP had significantly higher overall potency recovery rate compared with LRP (OR = 4.07, 95% CI 2.51–6.60, $P < 0.001$). Moreover, RARP was superior to LRP in terms of potency recovery rate at 3 (OR = 4.25, 95% CI 1.67–10.82, $P = 0.002$), 6 (OR = 3.52, 95% CI 1.31–9.44, $P = 0.010$), and 12 months (OR = 3.59, 95% CI 1.78–7.27, $P < 0.001$) postoperatively. (Fig. S5–S14, Supplemental Digital Content 3, http://links.lww.com/JS9/A366).

From the results of the quantitative synthesis of 21 non-randomised studies, the overall urinary continence recovery rate was 82.1% (2652 of 3229 cases) after LRP and 90.0% (5000 of 5558 cases) after RARP. The quantitative synthesis of the data showed that the overall continence recovery rate was higher in RARP

Table 1

Results of meta-analysis of RCTs and non-randomised studies.

	RCTs								Non-randomised studies							
		Sample size		Heterogeneity						Sample size		Heterogeneity				
Outcomes	No. studies	RARP	LRP	I^2 (%)	*P* value	Overall effect size	95% CI of overall effect	*P* value	No. studies	RARP	LRP	I^2 (%)	*P* value	Overall effect size	95% CI of overall effect	*P* value
Operation time (min)	2	590	248	0	0.380	WMD = 5.64	0.34–10.94	0.040	24	3296	2135	98	< 0.001	WMD = 3.00	− 14.05 to 20.05	0.730
Blood loss (ml)	2	590	248	80	0.020	WMD = 2.95	− 56.84 to 62.74	0.920	19	2742	1787	91	< 0.001	WMD = − 71.99	− 99.37 to − 44.61	< 0.001
Catheterization duration (day)	3	642	308	77	0.010	WMD = − 0.34	− 1.31 to 0.64	0.500	13	1742	986	92	< 0.001	WMD = − 1.03	− 1.84 to − 0.22	0.010
Length of hospital stay (day)						—			20	3673	2049	87	< 0.001	WMD = − 0.41	− 0.68 to − 0.13	0.004
Transfusion rate						—			17	3786	3139	32	0.110	OR = 0.44	0.35–0.56	< 0.001
Overall complication rate	3	674	319	50	0.140	OR = 0.87	0.60–1.25	0.440	25	5087	3782	54	< 0.001	OR = 0.72	0.54–0.96	0.020
Overall urinary continence rate	3	659	291	36	0.210	OR = 1.60	1.16–2.20	0.004	21	5558	3229	40	0.030	OR = 1.48	1.29–1.70	< 0.001
Urinary continence rate at 1 month	2	112	120	0	0.610	OR = 2.14	1.25–3.66	0.005	5	2048	1578	32	0.210	OR = 1.89	1.58–2.26	< 0.001
Urinary continence rate at 3 months	3	659	291	0	0.430	OR = 1.51	1.12–2.02	0.006	15	4222	2750	39	0.060	OR = 1.53	1.36–1.71	< 0.001
Urinary continence rate at 6 months	2	112	120	0	0.920	OR = 2.66	1.31–5.40	0.007	13	3182	2206	0	0.800	OR = 1.71	1.49–1.98	< 0.001
Urinary continence rate at 12 months	2	112	120	0	0.880	OR = 3.52	1.36–9.13	0.010	11	3764	2527	15	0.300	OR = 1.38	1.20–1.58	< 0.001
Urinary continence rate at 24 months						—			4	2409	1880	0	0.720	OR = 1.42	1.20–1.68	< 0.001
Urinary continence rate at 36 months						—			4	1389	484	0	0.870	OR = 1.92	1.43–2.57	< 0.001
Overall erectile function recovery rate	3	428	225	17	0.300	OR = 4.07	2.51–6.60	< 0.001	17	4299	2154	69	< 0.001	OR = 1.51	1.15–1.99	0.003
Potency recovery rate at 1 month	2	112	120	86	0.009	OR = 6.67	0.38–116.71	0.190	2	1371	914	86	0.008	OR = 2.23	0.83–5.99	0.110
Potency recovery rate at 3 months	3	346	196	72	0.030	OR = 4.25	1.67–10.82	0.002	11	2781	1711	47	0.040	OR = 2.00	1.69–2.36	< 0.001
Potency recovery rate at 6 months	3	346	196	80	0.006	OR = 3.52	1.31–9.44	0.010	7	1567	1116	41	0.130	OR = 2.43	2.02–2.92	< 0.001
Potency recovery rate at 12 months	3	346	196	63	0.070	OR = 3.59	1.78–7.27	< 0.001	9	2586	1544	74	< 0.001	OR = 1.63	1.09–2.43	0.020
Potency recovery rate at 24 months						—			3	1550	1193	75	0.020	OR = 2.34	1.37–3.97	0.002
Potency recovery rate at 36 months						—			3	878	379	18	0.300	OR = 1.51	1.02–2.24	0.040
Overall PSM rate	3	642	308	0	0.980	OR = 1.48	1.01–2.18	0.050	34	7056	5379	43	0.004	OR = 1.12	1.03–1.22	0.010
≤ pT2 PSM rate	2	80	89	0	0.920	OR = 0.84	0.31–2.27	0.740	20	3471	2826	35	0.060	OR = 1.08	0.93–1.25	0.340
≥ pT3 PSM rate	2	31	30	0	0.780	OR = 2.93	1.00–8.55	0.050	20	1631	1287	27	0.130	OR = 1.30	1.10–1.54	0.002
BCR rate	2	614	259	0	0.520	OR = 1.40	0.85–2.32	0.190	13	3540	1448	14	0.310	OR = 0.78	0.66–0.92	0.004

BCR, biochemical recurrence; LRP, laparoscopic radical prostatectomy; OR, odds ratio; PSM, positive surgical margin; RARP, robot-assisted radical prostatectomy; RCT, randomised controlled trials; WMD, weighted mean difference.

than LRP (OR = 1.48, 95% CI 1.29–1.70, $P < 0.001$). The results of the quantitative synthesis of 17 non-randomised studies showed that the overall potency recovery rate was 55.6% (1197 of 2154 cases) in those who received LRP and 66.4% (2856 of 4299 cases) in those who received RARP, and the results were statistically significantly different between the two groups (OR = 1.51, 95% CI 1.15–1.99, $P = 0.003$). In addition, RARP was superior to LRP for urinary continence and potency recovery rates at 3, 6, 12, 24, and 36 months postoperatively. (Figs. S25–S38, Supplemental Digital Content 3, http://links.lww.com/JS9/A366).

Oncologic outcomes

The overall PSM results were available from three RCTs with a pooled OR of 1.48 (95% CI 1.01–2.18, $P = 0.050$) from fixed-effect model, with no heterogeneity ($I^2 = 0\%$). Besides, there was no significant differences in terms of ≤pT2 (OR = 0.84, 95% CI 0.31–2.27, $P = 0.740$) and ≥pT3 PSM rates (OR = 2.93, 95% CI 1.00–8.55, $P = 0.050$) between the two groups (Fig. S15-S17, Supplemental Digital Content 3, http://links.lww.com/JS9/A366). The results of the quantitative synthesis of 34 non-randomised studies including 12 435 cases showed that RARP was associated with higher overall PSM rate compared to LRP (OR = 1.12, 95% CI 1.03–1.22, $P = 0.010$). However, there was a moderate heterogeneity ($I^2 = 43\%$). In ≤pT2 PSM rate, RARP and LRP were similar (OR = 1.08, 95% CI 0.93–1.25, $P = 0.340$), but in ≥pT3 PSM rate, RARP was higher than LRP (OR = 1.30, 95% CI 1.10–1.54, $P = 0.002$) (Fig. S39–S41, Supplemental Digital Content 3, http://links.lww.com/JS9/A366).

Results of meta-analysis of RCTs showed that RARP and LRP were similar in terms of BCR rate (OR = 1.40, 95% CI 0.85–2.32, $P = 0.190$, $I^2 = 0\%$) (Fig. S18, Supplemental Digital Content 3, http://links.lww.com/JS9/A366). However, the results of the quantitative synthesis of non-randomised studies showed that the BCR rate of RARP was lower than that of LRP (OR = 0.78, 95% CI 0.66–0.92, $P = 0.004$, $I^2 = 14\%$) (Fig. S42, Supplemental Digital Content 3, http://links.lww.com/JS9/A366).

Subgroup analysis

The results of subgroup analysis are summarised in Table S3, Supplemental Digital Content 3, http://links.lww.com/JS9/A366. Forest plots for subgroup analysis are shown in the Supplementary Material (Fig. S43–S59), Supplemental Digital Content 3, http://links.lww.com/JS9/A366. From the results of the pooled analysis of the PSMA subgroup, it was found that there were no significant differences in operative time (WMD = 40.37, 95% CI – 9.01 to 89.75, $P = 0.110$), blood loss (WMD = – 30.56, 95% CI – 90.10 to 28.98, $P = 0.310$), catheterization duration (WMD = – 1.16, 95% CI – 2.92 to 0.59, $P = 0.190$), hospital stay (WMD = – 0.51, 95% CI – 1.20 to 0.18, $P = 0.150$), transfusion rate (OR = 0.55, 95% CI 0.25–1.20, $P = 0.130$), overall complication rate (OR = 0.85, 95% CI 0.44–1.62, $P = 0.620$), urinary continence recovery rate at 12 months (OR = 1.74, 95% CI 0.61–4.99, $P = 0.300$), overall potency recovery rate (OR = 1.28, 95% CI 0.64–2.59, $P = 0.490$), potency recovery rate at 3 (OR = 1.69, 95% CI 0.75–3.79, $P = 0.210$) and 12 months (OR = 1.28, 95% CI 0.64–2.59, $P = 0.490$), ≤pT2 (OR = 1.23, 95% CI 0.91–1.66, $P = 0.180$) and ≥pT3 PSM rates (OR = 1.35, 95% CI 0.90–2.01, $P = 0.150$) as well as BCR rate (OR = 0.83, 95% CI 0.49–1.42, $P = 0.500$) between the groups of RARP and LRP. Moreover, RARP was higher than LRP in terms of overall continence recovery rate (OR = 2.24, 95% CI 1.06–4.75, $P = 0.030$), continence rates at 3 (OR = 2.07, 95% CI 1.17–3.64, $P = 0.010$) and 6 months (OR = 1.82, 95% CI 1.14–2.89, $P = 0.010$), and overall PSM rate (OR = 1.28, 95% CI 1.05–1.54, $P = 0.010$).

For the non PSMA subgroup, the results of the pooled analysis showed that there were no significant differences in terms of operative time (WMD = – 5.93, 95% CI – 24.14 to 12.28, $P = 0.520$), overall (OR = 1.08, 95% CI 0.98–1.19, $P = 0.120$) and ≤pT2 PSM rates (OR = 1.03, 95% CI 0.87–1.22, $P = 0.740$). However, there was statistical significance in blood loss (WMD = – 85.88, 95% CI – 119.14 to – 52.61, $P < 0.001$), hospital stay (WMD = – 0.38, 95% CI – 0.71 to – 0.05, $P = 0.030$), BCR rate (OR = 0.77, 95% CI 0.64–0.93, $P = 0.005$), overall complication rate (OR = 0.68, 95% CI 0.49–0.95, $P = 0.020$) and continence recovery rate (OR = 1.46, 95% CI 1.27–1.68, $P < 0.001$) as well as all remaining outcomes between RARP and LRP.

Sensitivity analysis

The results of the sensitivity analysis of RCTs and non-randomised studies are summarised in Table S4, Supplemental Digital Content 3, http://links.lww.com/JS9/A366 and Table S5, Supplemental Digital Content 3, http://links.lww.com/JS9/A366, respectively. Forest plots for sensitivity analysis are shown in the Supplementary Material (Fig. S60–S95), Supplemental Digital Content 3, http://links.lww.com/JS9/A366.

Sensitivity analysis of RCTs showed that the statistical results for each outcome were unchanged compared with the results of the overall pooled analysis, but the heterogeneity between studies was reduced in terms of catheterization duration, overall complication rate, overall continence recovery rate, overall potency recovery rate as well as potency recovery rate at 3, 6, and 12 months. When we performed sensitivity analysis for non-randomised studies, neither heterogeneity nor statistical results changed significantly in operative time, blood loss, catheterization duration and hospital stay compared with the overall pooled analyses. The statistical results for remaining outcomes were also unchanged, but heterogeneity among studies decreased.

Publication of bias

The funnel plots of included RCTs appeared symmetrical suggesting no publication bias. The symmetrical funnel plots of the non-randomised studies suggested that there were no obvious publication bias. Funnel plots are shown in the Supplementary Material (Fig. S96–S97), Supplemental Digital Content 3, http://links.lww.com/JS9/A366.

Discussion

To our knowledge, our study is the first to include a separate pooled analysis of RCTs and non-randomised studies. This systematic review and meta-analysis on the efficacy and safety of RARP in PCa highlights the great potential of RARP to improve perioperative, functional and oncologic outcomes, especially functional outcomes.

Concerning functional outcomes, the most common factors affecting quality of life after RP are urinary continence recovery

and erectile function recovery, which are also the most important concern of patients[71]. Both meta-analysis of RCTs and quantitative synthesis of non-randomised studies suggested that RARP had significant advantages over LRP in both urinary continence and erectile function recovery rates at 3, 6, and 12 months postoperatively. In addition, the results of quantitative synthesis of non-randomised studies also showed that RARP was still superior to LRP in terms of urinary continence and erectile function recovery rates at 24 and 36 months postoperatively. These results are consistent with the 5-year outcomes for their previously published prospective RCT comparing RARP and LRP by Porpiglia *et al*[72]. In their article, Porpiglia *et al.*[72] also reported continence and erectile function recovery data at 18, 30, 42, 48, 54, and 60 months postoperatively, which showed that RARP was significantly better than LRP. For the whole follow-up period, compared to the LRP group, the probability of achieving continence and potency over time was more than doubled in the RARP group, respectively (Continence: OR = 2.47, 95% CI 1.15–5.31, $P = 0.021$; Potency: OR = 2.35, 95% CI 1.10–5.03, $P = 0.028$)[72]. This can be explained by the fact that the Da Vinci robotic system allows the surgeon to more comfortably perform all steps that affect functional outcomes, such as nerve sparing, enhanced preservation of membranous urethra, and reconstruction of the bladder neck[30].

In addition, several previous studies suggested that surgical technique might also affect functional recovery of patients after surgery[31,47,50]. They believed that compared with LRP, the robotic platforms had the advantages of improved surgical vision and increased precision for preserving of neurovascular structures, which could greatly improve functional recovery after RARP. Paulo *et al.*[73] proposed a technical improvement for RARP, namely retrograde release of the neurovascular bundle with preservation of dorsal venous complex during RARP. Their results showed that urinary continence recovery and erectile function recovery rates were 98.4% and 86.7% at 1 year postoperatively, respectively. A recent study described a novel surgical technique of urethral fixation during RARP[74]. Their results showed that the use of the new urethral fixation technique during RARP significantly improved early continence recovery compared with standard vesicoureteral anastomosis (97.1% vs. 80%) without increasing operating room time or perioperative complications. Moreover, the findings of Salciccia *et al.*[75] revealed that operative time represented a significant variable able to affect the functional outcome of patients after surgery. The incidence of erectile dysfunction gradually increased with the operative time, but operative time was not independent to other variables (age and nerve-sparing procedure).

The main goal of RP is cancer control. In our study, we observed that RARP had similar or even higher PSM rate than LRP, which is consistent with previously published results[11]. Previous studies shown that BMI, surgical experience, larger prostate volume, PSA, Gleason score, and pathological stage were significant independent predictors of PSM[44,45,55,60,76,77]. The study by Bursh *et al.*[54] also confirmed that obesity had a detrimental effect on the pathological outcome after RP. Considered by Asimakopoulos *et al.*[77] as the only modifiable factor influencing PSM rate, surgical experience was identified as a key factor for high-quality oncologic outcomes. A systematic review published by Yosepovich *et al.*[76] reported that the PSM rate in RARP was higher in patients with a more advanced pathological stage. To explore other factors affecting PSM, Salciccia and colleagues enroled 413 patients undergoing RP, 67% of whom received LRP and 33% received RARP, and analysed whether operative time and blood loss during RP can significantly affect surgical margin status[75]. Their results showed that PSM rate was significantly associated with operative time, and higher PSM rate was found in cases with operative time <120 min (41.2%) and >240 min (53.4%). Patients with an operation time <120 minutes and >240 minutes had 1.70 and 1.94 times increased risk of PSM, respectively. To reduce the risk of PSM incidence, some recent studies have attempted to introduce a 3D augmented reality model in the NS phase of RARP[78–80]. This new proposed technique enables surgeons to perform a 3D augmented reality RARP, which allows distinguishing the index lesion in real time and directing the intraoperative frozen section analysis aimed to reduce PSM rate at the level of the index lesion.

Theoretically, for resectable PCa, the presence of PSM is associated with BCR. In the studies by Kim *et al.*[81] and Asimakopoulos *et al.*[77], multivariate analysis showed that PSA, PSM, pathological stage, and Gleason score were significant independent predictors of BCR. However, in our study, we observed lower BCR rate in patients receiving RARP. One conclusion that can be drawn from the study by Choo *et al.*[82] is that similar PSM rates do not imply similar BCR rates. In addition, Meguro *et al.*[83] reported that in multivariate analyses, operative time was significantly associated with BCR, with a cut-off value of 228.5 min for operative time. They suggested that prolonged operative time was associated with BCR in patients with positive surgical margins. Therefore, operative time should be limited as much as possible to reduce surgical stress, which may lead to BCR. In a previously published study, Pushan *et al.*[84] reported that blood transfusion increased the BCR in patients undergoing RP. From this, we hypothesised that the high precision and low destructiveness of robotic surgery resulted in lower intraoperative blood transfusion rates, which in turn demonstrated lower postoperative BCR rates in patients receiving RARP. Of course, this requires a series of prospective studies to verify.

The quantitative synthesis of non-randomised studies showed a stronger treatment effect of RARP than meta-analysis of RCTs in terms of perioperative and oncologic outcomes. There are several reasons for the stronger effect suggested by non-randomised studies. First, the potential for confounding by other factors must be kept in mind. For example, the time distribution of receiving RARP and LRP was different, which was manifested in the fact that when the patient received RARP, the surgeon who performed the operation had performed multiple cases of LRP. Surgeons with extensive experience in laparoscopic surgery could achieve better outcomes after, or even during, the learning curve with the inherent advantages of robotic surgical system[85,86]. Secondly, with the continuous improvement of technology in recent years, the continuous optimisation of the system, and the continuous updating of concepts, more and more people chose robotic surgery for treatment, especially in high-volume hospitals, which made the surgical volume of RARP continue to increase and experience continue to grow, thereby enabling RARP to exhibit a stronger therapeutic effect[87].

Our systematic review and meta-analysis have several limitations. First, we cannot definitively rule out publication bias, even if there is no associated indication of publication bias in the funnel plots. Furthermore, in both RCTs and non-randomised studies, there is substantial heterogeneity among studies. Although

statistical heterogeneity was observed in the quantitative synthesis of non-randomised studies, the results remained largely unchanged (but heterogeneity was strongly reduced) when sensitivity analysis was performed. Finally, the number of RCTs available so far is small and of varying quality, so there is insufficient evidence to support or refute the use of one technique over another.

Conclusion

The present meta-analysis suggests that RARP can improve functional outcomes compared with LRP. Moreover, RARP has potential advantages in perioperative and oncologic outcomes. High-quality, multi-centre RCTs with standardized experimental designs and results reporting are also needed in the future, especially with regard to random assignment concealment, blinded implementation and longer follow-up periods. Non-randomised studies should address other issues primarily relevant to clinical practice, such as propensity score matching based on patient preoperative characteristics, to reduce risk of bias.

Ethical approval

IRB approval was not needed because this is a meta-analysis of published data; however, PROSPERO registration was done.

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Author contribution

Study design: J.M. Data collections: J.M., Y.Z., Y.W. Data analysis: W.C., G.J., J.R., X.Y., Q.H. Writing: J.M., W.X., R.C. Supervision: Y.C., S.R. Review and editing and final approval: All authors.

Conflicts of interest disclosure

None.

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2. Unique Identifying number or registration ID: CRD420-22330470.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022330470

Guarantor

Shancheng Ren.

Data statement

Data used in the conduction of this systematic review and meta-analysis will be available upon reasonable request from the corresponding author.

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