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Platinum Priority – Review – Prostate Cancer

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Positive Surgical Margin and Perioperative Complication Rates of Primary Surgical Treatments for Prostate Cancer: A Systematic Review and Meta-Analysis Comparing Retropubic, Laparoscopic, and Robotic Prostatectomy

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Abstract

Context: Radical prostatectomy (RP) approaches have rarely been compared adequately with regard to margin and perioperative complication rates.

Objective: Review the literature from 2002 to 2010 and compare margin and perioperative complication rates for open retropubic RP (ORP), laparoscopic RP (LRP), and robot-assisted LRP (RALP).

Evidence acquisition: Summary data were abstracted from 400 original research articles representing 167 184 ORP, 57 303 LRP, and 62 389 RALP patients (total: 286 876). Articles were found through PubMed and Scopus searches and met a priori inclusion criteria (eg, surgery after 1990, reporting margin rates and/or perioperative complications, study size >25 cases). The primary outcomes were positive surgical margin (PSM) rates, as well as total intra- and perioperative complication rates. Secondary outcomes included blood loss, transfusions, conversions, length of hospital stay, and rates for specific individual complications. Weighted averages were compared for each outcome using propensity adjustment.

Evidence synthesis: After propensity adjustment, the LRP group had higher positive surgical margin rates than the RALP group but similar rates to the ORP group. LRP and RALP showed significantly lower blood loss and transfusions, and a shorter length of hospital stay than the ORP group. Total perioperative complication rates were higher for ORP and LRP than for RALP. Total intraoperative complication rates were low for all modalities but lowest for RALP. Rates for readmission, reoperation, nerve, ureteral, and rectal injury, deep vein thrombosis, pneumonia, hematoma, lymphocele, anastomotic leak, fistula, and wound infection showed significant differences between groups, generally favoring RALP. The lack of randomized controlled trials, use of margin status as an indicator of oncologic control, and inability to perform cost comparisons are limitations of this study.

Conclusions: This meta-analysis demonstrates that RALP is at least equivalent to ORP or LRP in terms of margin rates and suggests that RALP provides certain advantages, especially regarding decreased adverse events.

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1. Introduction

Prostate cancer is the most common nondermatologic cancer in Western men [1]. More than 90% of cases are diagnosed when the disease is organ confined and potentially curable by radical prostatectomy (RP) [2]. This was traditionally performed by open retropubic RP (ORP), although minimally invasive surgery (MIS; conventional laparoscopic and robot-assisted laparoscopic RP, LRP and RALP, respectively) has become popular recently. There is substantial evidence of lower bleeding rates for MIS [3–6] but no good evidence of an overall benefit for one modality over another, and it is uncertain whether MIS, especially robotics, justifies its increased costs and training requirements [7].

The most important outcomes to assess when comparing ORP, LRP, and RALP are cancer control, complications, urinary continence, and sexual potency. Unfortunately, biochemical recurrences, metastases, and survival statistics, as well as continence and potency, require long-term follow-up to assess and can be subject to significant reporting and interpretational biases. Positive surgical margin (PSM) and perioperative complication rates thus remain early outcome measures of importance in comparing surgical modalities. Accrual to randomized controlled studies (RCTs) has been notoriously poor [3] with only one such trial reported comparing ORP and LRP [8]. In addition, of the thousands of

papers published on the surgical treatment of prostate cancer with radical prostatectomy, there have been relatively few comparative studies. A recent review found 37 comparative studies: 23 ORP and LRP, 10 ORP and RALP, and 4 LRP and RALP [9]. Meta-analyses based solely on comparative articles [9–11], although informative, do not represent most of the literature available in this area, which are single cohort studies. Also, these reports do not adequately adjust for differences between surgical cohorts. Therefore we performed a meta-analysis of all of the available peer-reviewed observational studies, controlling for differences between ORP, LRP, and RALP cohorts with propensity score adjustments [12,13], a technique used by other authors [14–17].

2. Evidence acquisition

The methods used in reporting this meta-analysis follow those outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18] (see Appendix 1, available online). The study design, search strategy, data abstraction, and excluded studies (with justification) are detailed in Table 1, Figure 1 [19–22], Appendix 2 (citations for excluded studies, available online), and Figure 2 (early experience analysis). PubMed and Scopus (2002–2010, English) were searched for original research

Table 1 – Study design

Patients	Patients undergoing RALP, LRP, or RRP for the primary treatment of localized prostate cancer
Literature search	Keyword search in PubMed and Scopus
Databases	PubMed and Scopus
Limits	Published from January 2002 to December 2010 (no limits on article type)
	Humans
	In English
Keywords	Retropubic radical prostatectomy Open prostatectomy RRP Laparoscopic assisted radical prostatectomy Laparoscopic radical prostatectomy LRP Endoscopic extraperitoneal radical prostatectomy EERPE Robotic assisted radical prostatectomy Robotic assisted laparoscopic prostatectomy RALP
Search details for sample PubMed search of EERPE	EERPE[All Fields] AND ("humans"[MeSH Terms] AND English[lang] AND ("2002/01/01"[PDAT]: "2010/12/31"[PDAT]))
Eligibility criteria	Full-text article (no abstracts) Unique publication (no duplicate articles) Reported on outcomes of interest (surgical margins, complications) Reported on at least 25 patients Original report as determined from reading the abstract or if necessary the full text; PubMed classifications were not used because they are not consistently available (no letters to the editor, editorials, comments, news articles, review articles, or meta-analyses) Outcome reported in a usable form (each surgical approach was reported as a separate cohort, no additional confounding treatments, no missing or unreliable data; could not have >10% difference in values between text and tables) Reported on surgical approaches of interest (no perineal prostatectomy)
Exclusion criteria (see Appendix 2 and 3, available online)	Duplicate patient population, where some or all of the same patients were included in a different study reporting on the same parameters (prevents double counting) Surgery prior to 1990 when minimally invasive surgery became first available (prevents bias toward RRP) Early case experience (prevents bias toward approaches with more experienced surgeons)

Table 1 (Continued)

Data abstraction	<p>Articles needed to report only on a single outcome of interest to be included in the analysis. For articles that reported on a cohort of interest (ORP, LRP, RALP) as well as on other treatments (eg, cryoablation, HIFU), only the cohorts of interest were included</p> <p>Data were uniformly abstracted by four individuals into a custom electronic database with a predetermined list of variables. Each individual was responsible for the review and abstraction of approximately 25% of the articles under consideration. The data for 25% of the articles was double-entered by a second individual, and any discrepancies were resolved through repeated review and discussion prior to data analysis. The consistency and accuracy of data abstractions was independently verified for a random sampling of 40% of the articles, with an error rate <1% and no systematic errors. All errors found were corrected before analysis. All primary outcomes were then double-checked and any discrepancies resolved</p>
Primary outcomes	<p>Four types of variables were abstracted from each study: those necessary to determine inclusion and exclusion criteria, surgical approach, baseline patient characteristics, and clinical outcomes</p> <p>Positive surgical margins (overall, pT2, and pT3)</p> <p>Total intraoperative and total perioperative complication rates</p>
Secondary outcomes	<p>Estimated blood loss</p> <p>Blood transfusion rates</p> <p>Conversion rates</p> <p>Length of hospital stay</p> <p>Individual complication rates</p> <ul style="list-style-type: none"> Deaths Readmission Reoperation Neurovascular injuries Organ injuries Ileus Thromboembolism Pneumonia Myocardial infarction Hematoma Lymphocele Anastomotic leakage Fistula Bladder neck/anastomotic stricture Sepsis Wound infection
Controls for bias due to selective reporting within a study (outcome level)	<p>In instances where a variable was reported in subgroups, such as Gleason score (<7, 7, >7), intraoperative and postoperative complications, or pT2 and pT3 PSM rates, only articles reporting data for all subgroups were included to control for selective reporting within studies and to ensure that comparisons between surgical modalities and meaningful interpretation of the results could be made</p>
Controls for bias due to differences in discharge criteria	<p>Length of hospital stay was analyzed separately for studies performed in the United States and for studies performed outside the United States</p>
Controls for differences in complication reporting	<p>Calculated complication rates for each paper based on the number of patients experiencing at least one complication rather than on the number of complications. For example, a patient experiencing no intraoperative complications and multiple postoperative complications was counted once in the total perioperative complication rate and not at all in the intraoperative rate. A patient experiencing at least one intraoperative complication and at least one postoperative complication was counted once in the total intraoperative rate and once in the total perioperative complication rate, and each complication would also be included in the respective individual complication rate (if it was one of the ones on the list of individual complications). All injury complications were considered intraoperative and if this injury (eg, rectal injury) also resulted in a new postoperative complication (eg, ileus), that patient would qualify to be counted in both the intraoperative rate and in the perioperative rate</p> <p>Calculated complication rate based on all data given and specific criteria rather than using author-provided complication rates</p> <p>Limited complications included in this meta-analysis to those reported for the perioperative period, excluding those identified as late complications (occurring after 30 d) for consistency in reporting (only 23/400 [5.75%] of papers reported complications beyond 30 d)</p>
Publication bias	<p>Reported individual complications to address some of the issues with pooling overall complication rates</p> <p>Included all studies published for each surgical approach; did not limit publications to high-volume centers or centers of excellence</p>
Control for bias when surgical modality outcomes are compared	<p>Performed a funnel plot analysis (see Fig. 4)</p> <p>Performed propensity score adjustments to account for differences in patient characteristics</p>

HIFU = high-intensity focused ultrasound; PSM = positive surgical margin; ORP = open retropubic radical prostatectomy; RALP = robot-assisted laparoscopic prostatectomy; LRP = laparoscopic radical prostatectomy; RRP = retropubic radical prostatectomy.

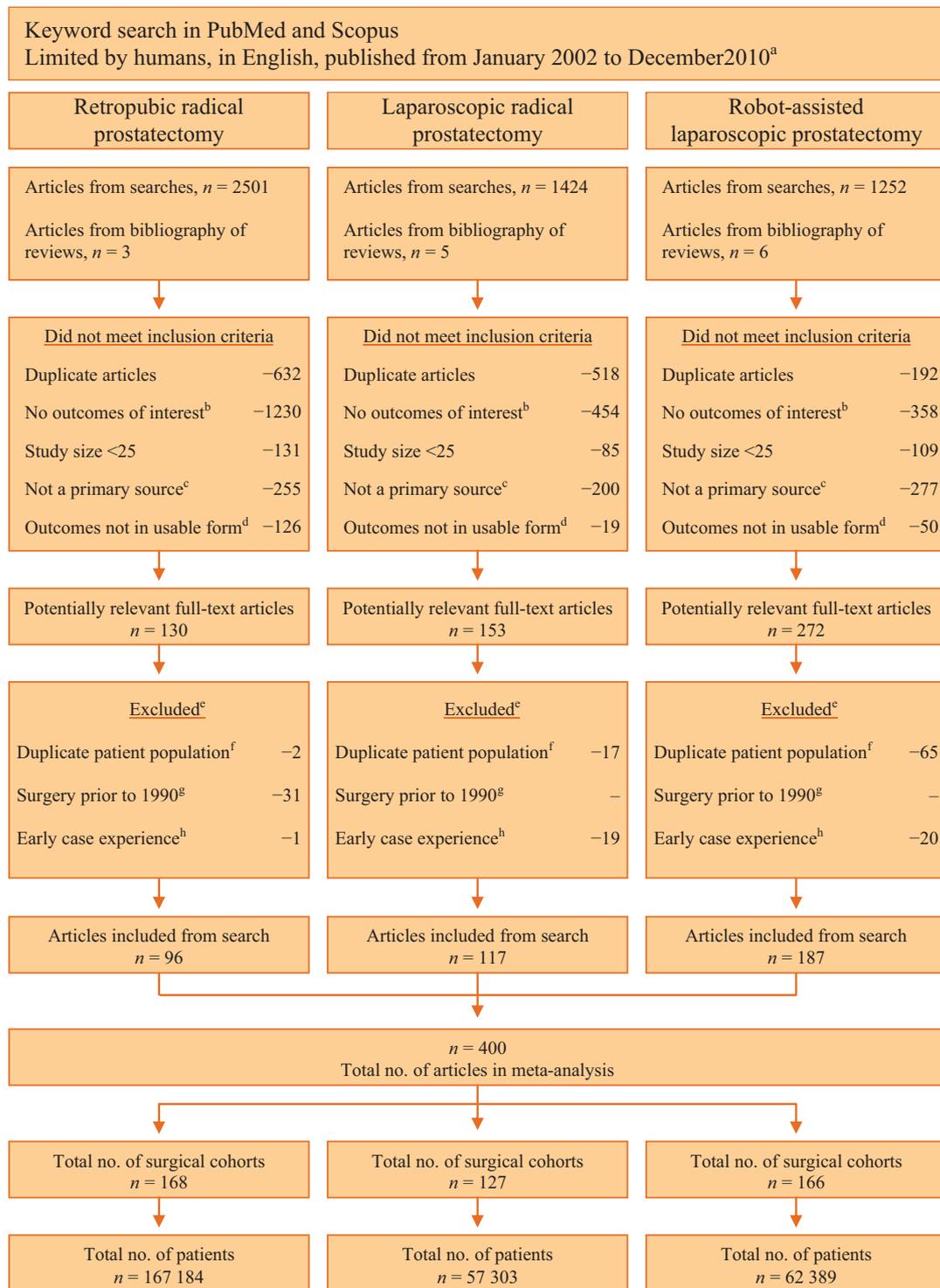


Fig. 1 – Flowchart outlining the literature search and article evaluation process.

^aAll inclusion and exclusion criteria were applied to each search in a uniform manner.

^bThe last search was completed in March 2011.

^cRepresents articles that did not report on outcomes of prostate cancer treatment, articles that reported on alternative treatments for prostate cancer, and articles that did not report on margin or complication rates.

^dIncludes letters to the editor, editorials, comments, news articles, review articles, and meta-analyses.

^eIncludes articles in which outcomes were not stratified by surgical approach, articles with additional confounding treatments, and articles with incomplete or erroneous data (these controls were also applied at the level of outcomes). See Appendix 2 (available online) for a list of excluded studies.

^fExcluded articles where some or all of the same patients were included in a different study reporting on the same parameters.

^gExcluded articles where the surgery took place prior to 1990 when minimally invasive surgery was first available.

^hExcluded articles that reported on the early experience of a surgeon. We defined early experience as the first 75 cases for a surgeon for each approach based on reports of the number of cases required to reach a base level of competence with the robotic approach [19–22] and confirmed with a post hoc analysis of positive margin rates as a function of the number of robot-assisted laparoscopic prostatectomy, laparoscopic radical prostatectomy, or retropubic radical prostatectomy cases performed that showed a decrease in the variability of outcomes after 75 cases (see Fig. 2).

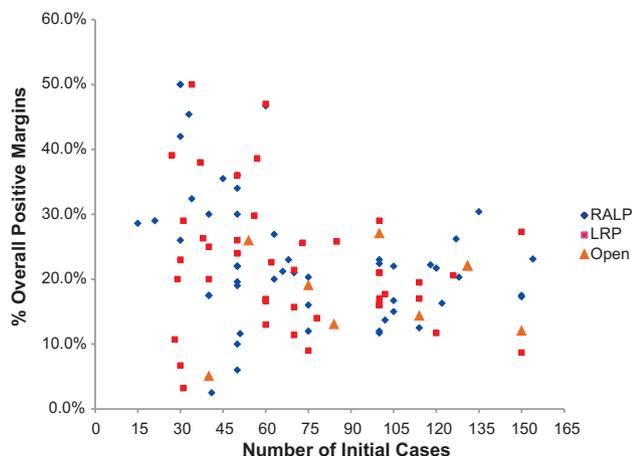


Fig. 2 – Early experience analysis. Graph showing the overall positive margin rate relative to the number of initial cases for robot-assisted laparoscopic radical prostatectomy (RALP; diamonds), laparoscopic radical prostatectomy (LRP; squares), and radical retropubic prostatectomy (Open; triangles).

articles reporting on the primary treatment of localized prostate cancer. We also reviewed the reference lists of prostatectomy review/meta-analysis articles and included those not already in our database [9,11,22,23].

All variables abstracted were chosen a priori for analysis. The main variables abstracted were surgical approach (retropubic [open], laparoscopic, robotic), type of publication (comparative series, single surgical method series) and publication year (2002–2010) (Tables 2a and 2b), patient characteristics (age, body mass index [BMI], preoperative prostate-specific antigen [PSA], preoperative Gleason score, and pathologic stage) (Table 3), and primary (positive surgical margin rates and total intra- and perioperative complication rates) and secondary outcomes (estimated blood loss [EBL], blood transfusions, conversions to ORP, length of stay [LOS], and specific individual complication rates; Tables 4–7). Follow-up was the perioperative period, defined as the time during surgery (intraoperative) and encompassing the first 30 d following surgery. Primary outcomes included measurement of efficacy (pT2, pT3, and overall PSM rates) and safety (total intraoperative and total perioperative complication rates). Secondary outcomes included changes in PSM rates over time, EBL, transfusion and conversion rates, and hospital LOS separated into US studies and non-US studies due to differences in discharge policies and individual complication rates (percentage of patients in a cohort experiencing the complication considered within 30 d of surgery).

2.1. Statistical methods

Patient characteristics and outcomes were summarized with descriptive statistics using weighted averages and weighted standard deviations with individual cohort size as the weight. Surgical approaches were contrasted in a pairwise manner using two sample *t* tests with Hochberg

Table 2a – Summary of study type

Study type	No. of papers	No. of cohorts by surgical method		
		ORP	LRP	RALP
Comparative articles				
RALP vs LRP vs ORP ^a	9	9	3	3
RALP vs LRP ^b	7		7	4
RALP vs ORP ^c	38	37		29
LRP vs ORP ^d	34	29	28	
Total No. of comparative articles	88 ^e	75	38	36
Single surgical method articles				
RALP	130			130
LRP	89		89	
ORP	93	93		
Total	400	168	127	166

ORP = open retropubic radical prostatectomy; LRP = laparoscopic radical prostatectomy; RALP = robot-assisted laparoscopic radical prostatectomy.
^a Six RALP/LRP combined cohorts were excluded.
^b Three RALP cohorts were excluded due to early experience.
^c Nine RALP cohorts (five early experience, four duplicate patient population) and one ORP cohort were excluded.
^d Includes one prospective randomized study (Appendix 3, Included Studies, reference 25, available online). Six LRP (five early experience, one duplicate patient population) and five ORP (three surgery too old, one small *n*, one no data) cohorts were excluded.
^e The percentage of comparative articles over time was 3.8% for 2002–2004, 24.4% for 2005–2006, 21.9% for 2007–2008, and 18.4% for 2009–2010.

Table 2b – Publication dates of included articles

Year of publication	ORP <i>n</i> (%)	LRP <i>n</i> (%)	RALP <i>n</i> (%)
2002–2004 ^a	21 (12.5)	23 (18.1)	2 (1.2)
2005–2006	12 (7.2)	27 (21.3)	14 (8.4)
2007–2008	54 (32.1)	36 (28.3)	43 (25.9)
2009–2010	81 (48.2)	41 (32.3)	107 (64.5)
No. of cohorts (total: 461)	168	127	166
No. of patients (total: 286 876)	167 184	57 303	62 389

Mantel-Haenszel chi-square test for overall difference in the rate of publications across the three cohorts over time, *p* < 0.0001.
^a Post hoc pairwise comparison: ORP vs LRP, *p* = 0.18; ORP vs RALP, *p* < 0.0001; LRP vs RALP, *p* < 0.0001.

correction for multiple comparisons. The three pairwise comparisons were RALP versus LRP, RALP versus ORP, and LRP versus ORP. The Hochberg method was implemented as follows: All three comparisons were significant if each had a *p* value ≤ 0.05; if one of the three comparisons was not significant (*p* > 0.05), then the other two were significant if they each had a *p* value ≤ 0.025; if two of three comparisons were not significant (*p* > 0.05), then the remaining one was significant if it had a *p* value < 0.017.

Because current literature contains almost entirely noncontrolled single institutional studies, cohorts of surgical methods to be compared often differ in terms of demographic and tumor characteristics. The statistical significance of outcomes between cohorts was adjusted for these differences using propensity score analysis. Propensity score analysis directly addresses the key problem of observational

Table 3 – Patient characteristics

Characteristic	ORP	LRP	RALP	p value ^a
Age, yr				
Cohorts (patients), n	150 (128 197)	111 (48 654)	155 (61 310)	0.72
Mean (SD)	61.8 (2.1)	61.7 (2.4)	60.6 (1.6)	<0.0001*
95% CI	61.5–62.1	61.3–62.1	60.3–60.9	<0.0001*
BMI (kg/m ²)				
Cohorts (patients), n	47 (28 828)	40 (21 150)	100 (40 154)	0.009*
Mean (SD)	27.3 (0.9)	26.7 (1.2)	27.3 (1.0)	1.00
95% CI	27.0–27.6	26.3–27.1	27.1–27.5	0.003*
Preoperative PSA, ng/ml				
Cohorts (patients), n	120 (68 470)	107 (49 571)	135 (54 613)	0.25
Mean (SD)	7.5 (2.9)	7.9 (2.3)	6.3 (1.7)	<0.0001*
95% CI	7.0–8.0	7.5–8.3	6.0–6.6	<0.0001*
Preoperative Gleason score, %				
<7				
Cohorts (patients), n	74 (63 095)	43 (30 596)	79 (40 884)	0.06
Mean (SD)	58.9 (13.1)	54.3 (11.4)	52.8 (15.9)	0.01*
95% CI	55.9–61.9	50.9–57.7	49.3–56.3	0.55
=7				
Cohorts (patients), n	74 (63 095)	43 (30 596)	79 (40 884)	0.05
Mean (SD)	34.1 (11.9)	38.4 (9.7)	39.9 (14.0)	0.007*
95% CI	31.4–36.8	35.5–41.3	36.8–43.0	0.49
>7				
Cohorts (patients), n	74 (63 095)	43 (30 596)	79 (40 884)	0.74
Mean (SD)	7.0 (4.7)	7.3 (4.6)	7.3 (6.4)	0.74
95% CI	5.9–8.1	5.9–8.7	5.9–8.7	1.00
Pathologic stage, % ^b				
pT2				
Cohorts (patients), n	111 (79 193)	105 (47 802)	113 (43 558)	0.12
Mean (SD)	68.8 (8.8)	70.9 (10.9)	78.8 (9.1)	<0.0001*
95% CI	67.2–70.4	68.8–73.0	77.1–80.5	<0.0001*
pT3				
Cohorts (patients), n	111 (79 193)	104 (47 235)	112 (43 273)	0.10
Mean (SD)	28.6 (7.5)	26.8 (8.4)	20.1 (7.5)	<0.0001*
95% CI	27.2–30.0	25.2–28.4	18.7–21.5	<0.0001*

ORP = open retropubic radical prostatectomy; LRP = laparoscopic radical prostatectomy; RALP = robot-assisted laparoscopic radical prostatectomy; SD = standard deviation; CI = confidence interval; BMI = body mass index; PSA = prostate-specific antigen.

^a The p values are reported in the following order: ORP vs LRP, ORP vs RALP, LRP vs RALP.

^b pT2 and pT3 values do not include pT0 or pT4.

* Significant at 5% level after adjusting for multiple comparisons (Hochberg correction).

group comparisons: that of differences in patient selection criteria. First, covariates were selected that might distinguish between the surgical cohorts to be compared and have a relationship with outcome variables. Overall PSM rates were adjusted for preoperative Gleason score, preoperative PSA, and pathologic stage; pT2 and pT3 PSM rates were adjusted for preoperative Gleason score and preoperative PSA; all perioperative outcomes and complication rates were adjusted for age, BMI, preoperative Gleason score, preoperative PSA, and pathologic stage. A multivariate logistic regression modeling of the probability of being in a cohort treated with either of two surgical methods to be compared (there are three such pairwise models) yielded estimated propensity scores, where the propensity score was defined as the probability of being in either type of surgical cohort, conditioned on the average covariate values for that cohort. Second, study cohort propensity scores (from both surgical methods) were ordered from smallest to largest and adjacent scores grouped into strata. Depending on the number of cohorts available to make comparisons, up to five strata were formed, usually sufficient to remove 90% of the selection bias [12]. Within each derived stratum, surgical methods were

compared using a difference in average outcome. Propensity score analysis yielded covariate distributions that are similar across cohorts to be compared within each stratum [13]. A Cochran-Mantel-Haenszel weight was then calculated for each stratum. The adjusted summary measure of difference between surgical methods was computed as the weighted average of differences of the surgical methods across strata. The weighted standard error across strata was also calculated, and pairwise comparisons were evaluated using standard normal theory. For each outcome for each surgical method, two different adjusted rates were calculated because the value of the adjusted rate depends on the pair of surgical methods being compared. The size of the adjustment was larger when there was a larger difference in preoperative characteristics included in the propensity score model. Because the adjusted rates were not unique and inferences were based on the (uniquely) adjusted difference between pairs of surgical methods, only the differences in rates were reported after propensity score adjustment.

For a given surgical type, the I^2 statistic was used to quantify the percentage of variability in outcomes due to

Table 4 – Primary outcomes: comparison of positive surgical margin and overall complication rates

Primary outcome	Unadjusted estimates						Propensity-adjusted estimates					
	Weighted averages			Unadjusted <i>p</i> value			Adjusted differences ^a			Adjusted <i>p</i> value		
	ORP	LRP	RALP	ORP vs LRP	ORP vs RALP	LRP vs RALP	ORP minus LRP	ORP minus RALP	LRP minus RALP	ORP vs LRP	ORP vs RALP	LRP vs RALP
PSM rate												
Overall PSM, %												
Cohorts (patients), <i>n</i>	61 (47 103)	81 (33 180)	73 (28 950)				2.24	0.29	3.02	0.13	0.79	0.002 [*]
Mean (SD)	24.2 (9.8)	20.4 (5.0)	16.2 (5.6)	0.007 [*]	<0.0001 [*]	<0.0001 [*]	–0.7 to 5.2	–1.9 to 2.4	1.1–5.0			
95% CI	21.7–26.6	19.3–21.5	14.9–17.5									
pT2 PSM, %												
Cohorts (patients), <i>n</i>	61 (47 103)	81 (33 180)	73 (28 950)				0.15	0.17	2.54	0.57	0.86	0.01 [*]
Mean (SD)	16.6 (8.8)	13.0 (4.4)	10.7 (4.7)	0.004 [*]	<0.0001 [*]	0.002 [*]	–1.7 to 2.0	–1.7 to 2.0	0.5–4.6			
95% CI	14.4–18.8	12.0–14.0	9.7–11.7									
pT3 PSM, %												
Cohorts (patients), <i>n</i>	61 (47 103)	81 (33 180)	73 (28 950)				–2.97	–3.91	3.34	0.07	0.03	0.05
Mean (SD)	42.6 (14.4)	39.7 (8.8)	37.2 (10.2)	0.16	0.016 [*]	0.10	–6.2 to 0.2	–7.3 to –0.5	0.05–6.6			
95% CI	39.0–46.2	37.8–41.6	34.7–39.5									
Complication rates												
Total intraoperative												
Cohorts (patients), <i>n</i>	39 (16 647)	57 (16 389)	42 (14 309)				–0.32	1.15	1.10	0.93	<0.0001 [*]	<0.0001 [*]
Mean (SD)	1.5 (1.6)	1.6 (1.9)	0.4 (0.5)	0.79	0.0005 [*]	<0.0001 [*]	–1.0 to 0.4	0.7–1.6	0.7–1.5			
95% CI	1.0–2.0	1.1–2.1	0.4–0.7									
Total perioperative												
Cohorts (patients), <i>n</i>	39 (16 647)	57 (16 389)	42 (14 309)				5.24	13.76	6.74	0.08	<0.0001 [*]	0.002 [*]
Mean (SD)	17.9 (9.1)	11.1 (9.6)	7.8 (6.3)	0.0008 [*]	<0.0001 [*]	0.04 [*]	–0.7 to 11.1	9.5–18.0	2.6–10.9			
95% CI	15.0–20.8	8.6–13.6	5.9–9.7									

ORP = open retropubic radical prostatectomy; LRP = laparoscopic radical prostatectomy; RALP = robot-assisted laparoscopic radical prostatectomy; PSM = positive surgical margin; SD = standard deviation; CI = confidence interval; pT2 = organ-confined cancer (not including pT0); pT3 = non-organ-confined cancer (not including pT4).

^a Overall PSM values were adjusted for preoperative Gleason score, preoperative PSA, and pathologic stage; the pT2 and pT3 PSM values were adjusted for preoperative Gleason and preoperative PSA; complication rates were adjusted for age, BMI, preoperative Gleason score, preoperative PSA, and pathologic stage.

^{*} Significant at 5% level after adjusting for multiple comparisons (Hochberg correction).

Table 5 – Overall positive surgical margin rates over time

Year of publication	ORP	LRP	RALP
2002–2004	24.9 (12.5)	21.3 (4.2)	22.1 (1.0)
2005–2006	13.0 (4.8)	22.8 (5.6)	14.6 (4.4)
2007–2008	23.7 (11.0)	19.7 (5.6)	14.6 (3.5)
2009–2010	25.0 (6.7)	19.7 (4.7)	16.8 (6.0)
Overall positive surgical margins	24.2 (9.8)	20.4 (5.0)	16.2 (5.6)
<i>p</i> value*	0.38	0.66	0.38

ORP = retropubic radical prostatectomy; LRP = laparoscopic radical prostatectomy; RALP = robot-assisted laparoscopic radical prostatectomy.
Data are mean rates % (standard deviation).
* Jonckheere-Terpstra test.

differences between cohorts. This measure is based on the *Q* statistic, a weighted average of squared deviations of each cohort's outcome from the mean of their outcomes. The *I*² index quantifies the relative amount of heterogeneity between outcome values by comparing the value of the *Q* statistic with its expected value assuming homogeneity.

Additional analyses included a Mantel-Haenszel chi-square test to make an overall comparison and Fisher exact tests to check for pairwise differences in publications by year between surgical approaches. The Jonckheere-Terpstra test was used to check for changes in positive margin rates over time. Funnel plot analysis was performed on overall PSM and total perioperative complication rates to check for publication bias (Fig. 4). All analyses were performed using SAS v.9.2.1 (SAS Institute, Cary, NC, USA).

Summary data were abstracted from 400 studies (Appendix 3, available online) that reported on 168 ORP, 127 LRP, and 166 RALP cohorts representing 167 184 ORP, 57 303 LRP, and 62 389 RALP patients (total: 286 876 patients).

3. Evidence synthesis

There were differences in the rate of publications across the three cohorts over time ($p < 0.0001$). Specifically, a statistically significantly greater proportion of ORP and LRP cohorts came from early publications (2002–2004) compared with RALP (12.5% and 18.1% vs 1.2%; ORP vs LRP, $p = 0.18$; ORP vs RALP, $p < 0.0001$; LRP vs RALP, $p < 0.0001$) (Tables 2a and 2b). There were differences in preoperative PSA between surgical cohorts, with the RALP cohort having a significantly lower average preoperative PSA than the ORP and LRP cohorts ($p < 0.0001$ for both comparisons) (Table 3). There were no significant differences in the percentage of high-grade disease (Gleason score >7) between the surgical approaches, although the ORP cohort (28.6%) and the LRP cohort (26.8%) had a significantly higher percentage of patients with pT3 disease than the RALP cohort (20.1%) ($p < 0.0001$ for both comparisons).

3.1. Primary outcomes (Fig. 3)

The overall PSM rates were 24.2% ORP, 20.4% LRP, and 16.2% RALP; pT2 PSM rates were 16.6% ORP, 13.0% LRP, and 10.7% RALP with only RALP versus LRP comparisons for overall and pT2 rates attaining significance after propensity score

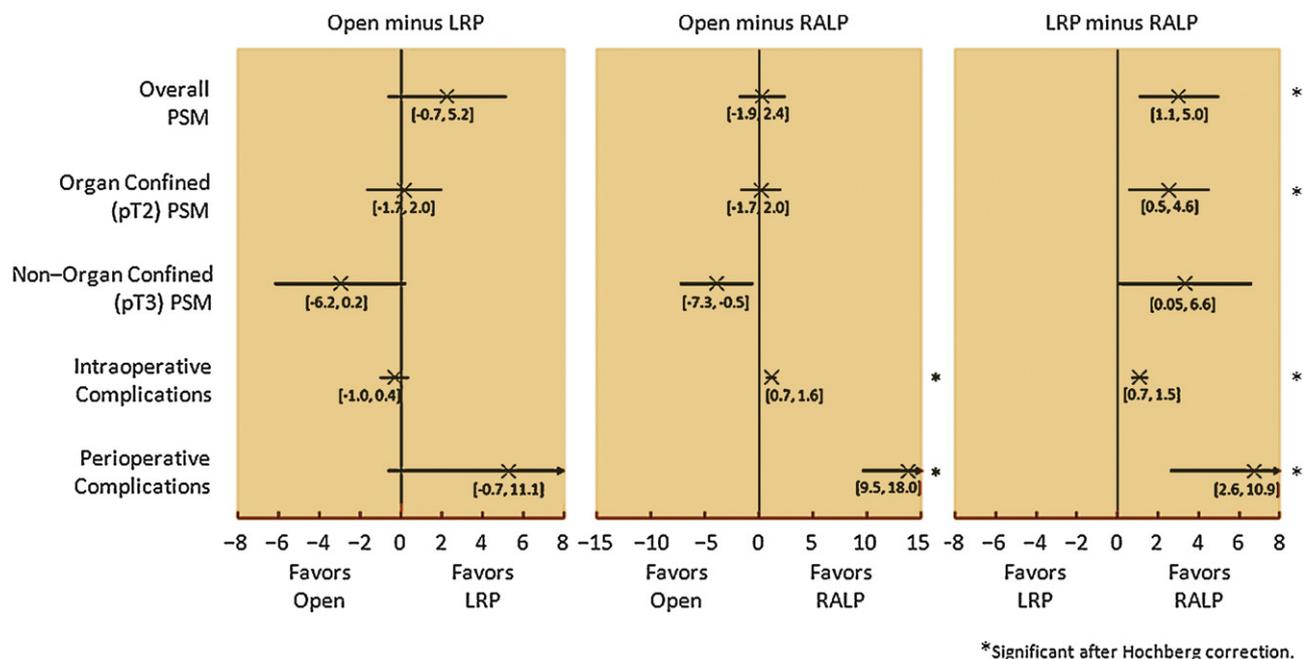


Fig. 3 – Modified forest plot showing propensity-adjusted differences (X) and 95% confidence intervals (horizontal lines and numbers in brackets) for the primary outcomes. The asterisks mark values that are significant after Hochberg correction (all three comparisons are significant if each has a p value ≤ 0.05 ; if one of three comparisons is not significant ($p > 0.05$), then the other two are significant if they each have a p value ≤ 0.025 ; if two of three comparisons are not significant ($p > 0.05$), then the other one is significant if it has a p value < 0.017). LRP = laparoscopic radical prostatectomy; Open = radical retropubic prostatectomy; PSM = positive surgical margin; pT2 = postoperative stage T2; pT3 = postoperative stage T3; RALP = robot-assisted laparoscopic radical prostatectomy.

Table 6 – Comparisons of perioperative outcomes

Perioperative outcomes	Weighted average						Propensity-adjusted estimates					
	Unadjusted estimates			Unadjusted <i>p</i> values			Adjusted differences ^a			Adjusted <i>p</i> value		
	ORP	LRP	RALP	ORP vs LRP	ORP vs RALP	LRP vs RALP	ORP minus LRP	ORP minus RALP	LRP minus RALP	ORP vs LRP	ORP vs RALP	LRP vs RALP
Estimated blood loss, ml												
Cohorts (patients), <i>n</i>	94 (31 492)	80 (24 688)	112 (41 672)									
Mean (SD)	745.3 (396.0)	377.5 (206.8)	188.0 (86.5)	<0.0001*	<0.0001*	<0.0001*	363.1	562.5	127.8	<0.0001*	<0.0001*	<0.0001*
95% CI	665.4–825.6	332.2–423.0	174.1–204.5				272.4–453.8	485.2–639.8	95.4–160.2			
Blood transfusions, %												
Cohorts (patients), <i>n</i>	85 (84 848)	79 (25 610)	70 (5849)									
Mean (SD)	16.5 (12.5)	4.7 (6.7)	1.8 (1.8)	<0.0001*	<0.0001*	0.006*	8.89	18.10	1.02	<0.0001*	<0.0001*	0.07
95% CI	13.9–19.1	3.2–6.0	1.5–2.3				4.8–13.0	14.6–21.6	–0.1 to 2.1			
Conversions to open, %												
Cohorts (patients), <i>n</i>		62 (19 707)	49 (23 232)									
Mean (SD)	NA	0.7 (1.3)	0.3 (0.6)	NA	NA	0.11	NA	NA	0.45	NA	NA	0.26
95% CI		0.4–1.0	0.2–0.6						–0.3 to 1.2			
LOS, United States, d												
Cohorts (patients), <i>n</i>	28 (32 970)	18 (5409)	48 (20 393)									
Mean (SD)	3.1 (0.5)	2.1 (0.3)	1.4 (0.4)	<0.0001*	<0.0001*	<0.0001*	0.97	1.69	0.78	<0.0001*	<0.0001*	<0.0001*
95% CI	2.9–3.3	2.0–2.2	1.3–1.5				0.8–1.2	1.5–1.9	0.7–0.9			
LOS, non–United States, d												
Cohorts (patients), <i>n</i>	36 (9319)	48 (16 654)	29 (4679)									
Mean (SD)	9.9 (4.6)	6.3 (3.0)	4.0 (1.3)	<0.0001*	<0.0001*	<0.0001*	1.83	3.65	1.04	0.008*	<0.0001*	0.005*
95% CI	8.4–11.4	5.5–7.2	3.5–4.4				0.5–3.2	2.8–4.5	0.3–1.8			

ORP = open retropubic radical prostatectomy; LRP = laparoscopic radical prostatectomy; RALP = robot-assisted laparoscopic radical prostatectomy; SD = standard deviation; CI = confidence interval; NA = not applicable; LOS = length of stay in hospital.

^a All perioperative outcomes adjusted for age, body mass index, preoperative Gleason score, preoperative prostate-specific antigen, and pathologic stage.

* Significant at 5% level after adjusting for multiple comparisons (Hochberg correction).

Table 7 – Intra- and perioperative complication rates

Complication, %	Unadjusted estimates			Unadjusted			Propensity-adjusted estimates					
	(weighted average)			<i>p</i> values			Adjusted difference ^a			Adjusted <i>p</i> value		
	ORP	LRP	RALP	ORP vs LRP	ORP vs RALP	LRP vs RALP	ORP minus LRP	ORP minus RALP	LRP minus RALP	ORP vs LRP	ORP vs RALP	LRP vs RALP
Deaths												
Cohorts (patients), <i>n</i>	43 (26 261)	48 (12 558)	26 (12 286)									
Mean (SD)	0.1 (0.1)	0.04 (0.14)	0.04 (0.1)	0.02 [*]	0.02 [*]	1.00	0.03	0.01	−0.008	0.40	0.62	0.80
95% CI	0.07–0.13	0.03–0.05	0.001–0.08				−0.04 to 0.08	−0.04 to 0.06	−0.07 to 0.05			
Readmission												
Cohorts (patients), <i>n</i>	6 (7548)	4 (725)	7 (4680)									
Mean (SD)	3.0 (2.6)	11.3 (6.0)	3.5 (2.2)	0.02 [*]	0.71	0.01 [*]	−9.45	4.16	6.77	0.006 [*]	<0.0001 [*]	0.0003 [*]
95% CI	0.9–5.1	5.4–17.2	1.9–5.1				−16.2 to 2.7	2.3–6.0	3.1–10.4			
Reoperation												
Cohorts (patients), <i>n</i>	31 (15 401)	32 (12 380)	28 (14 459)									
Mean (SD)	2.3 (1.3)	1.9 (1.1)	0.9 (1.0)	0.19	<0.0001 [*]	0.0005 [*]	0.35	0.30	0.97	0.33	0.32	0.0001 [*]
95% CI	1.8–2.8	1.5–17.2	1.9–5.1				−0.4 to 1.1	−0.3 to 0.9	0.5–1.5			
Vessel injury												
Cohorts (patients), <i>n</i>	7 (4595)	28 (12 196)	15 (10 567)									
Mean (SD)	0.04 (0.2)	0.4 (0.8)	0.08 (0.1)	0.04	0.63	0.05	−0.22	0.03	0.29	0.12	0.44	0.17
95% CI	−0.1 to 0.2	0.1–0.7	0.03–0.1				−0.50 to 0.06	−0.05 to 0.11	−0.12 to 0.71			
Nerve injury^b												
Cohorts (patients), <i>n</i>	14 (10 222)	25 (12 255)	21 (7015)									
Mean (SD)	0.4 (0.4)	2.0 (5.3)	0.4 (0.7)	0.15	1.00	0.15	−2.18	−0.006	8.70	0.18	0.98	0.0006 [*]
95% CI	0.2–0.6	−0.08 to 4.1	0.1–0.7				−5.3 to 1.0	−0.5 to 0.5	3.7–13.7			
Ureteral injury												
Cohorts (patients), <i>n</i>	18 (13 496)	30 (16 112)	16 (7402)									
Mean (SD)	1.5 (1.9)	0.2 (0.3)	0.1 (0.2)	0.01 [*]	0.006 [*]	0.24	0.68	1.74	0.10	0.02 [*]	0.012 [*]	0.19
95% CI	0.6–2.4	0.1–0.3	0.002–0.2				0.1–1.3	0.4–3.1	−0.05 to 0.2			
Bladder injury												
Cohorts (patients), <i>n</i>	6 (4306)	16 (7803)	12 (6190)									
Mean (SD)	0.05 (0.3)	0.4 (0.8)	0.07 (0.2)	0.15	0.87	0.13	−0.63	−0.03	0.06	0.07	0.63	0.74
95% CI	−0.2 to 0.3	0.008–0.8	−0.04 to 0.2				−1.3 to 0.05	−0.2 to 0.09	−0.03 to 0.4			
Rectal injury												
Cohorts (patients), <i>n</i>	35 (28 023)	52 (19 860)	29 (9453)									
Mean (SD)	0.5 (0.6)	1.0 (0.8)	0.3 (0.4)	0.002 [*]	0.12	<0.0001 [*]	−0.58	0.04	0.44	0.0002 [*]	0.76	0.0002 [*]
95% CI	0.3–0.7	0.8–1.2	0.2–0.4				−0.9 to −0.3	−0.2 to 0.3	0.2–0.7			
Bowel injury^c												
Cohorts (patients), <i>n</i>	5 (4206)	18 (11 798)	16 (11 606)									
Mean (SD)	0 (0)	0.07 (0.1)	0.09 (0.1)	0.009 [*]	0.003 [*]	0.56	−0.08	−0.09	−0.05	0.09	0.03	0.10
95% CI	–	0.02–0.1	0.04–0.14				−0.1 to 0.01	−0.2 to −0.1	−0.1 to 0.01			
Ileus												
Cohorts (patients), <i>n</i>	21 (7336)	35 (11 932)	32 (10 665)									
Mean (SD)	0.8 (1.4)	0.9 (1.0)	0.8 (0.9)	0.76	1.00	0.67	0.40	−0.23	0.40	0.14	0.36	0.11
95% CI	0.2–1.4	0.6–1.2	0.5–1.1				−0.1 to 0.9	−0.7 to 0.3	−0.08 to 0.9			
Deep vein thrombosis												
Cohorts (patients), <i>n</i>	26 (12 989)	27 (13 346)	27 (9753)									
Mean (SD)	1.0 (0.6)	0.5 (0.4)	0.3 (0.4)	0.0007 [*]	<0.0001 [*]	0.06	0.39	0.55	0.35	0.02 [*]	0.008 [*]	0.003 [*]
95% CI	0.8–1.2	0.4–0.6	0.1–0.5				0.06–0.7	0.1–1.0	0.1–0.6			

Pulmonary embolism												
Cohorts (patients), n	26 (12 767)	27 (99 996)	25 (10 415)									
Mean (SD)	0.5 (0.4)	0.4 (0.4)	0.3 (0.5)	0.37	0.12	0.43	−0.02	0.24	0.08	0.88	0.08	0.53
95% CI	0.3–0.7	0.2–0.6	0.1–0.5				−0.2 to 0.2	−0.02 to 0.5	−0.2 to 0.3			
Pneumonia												
Cohorts (patients), n	11 (8035)	13 (5426)	12 (5265)									
Mean (SD)	0.5 (0.6)	0.1 (0.2)	0.05 (0.1)	0.06	0.03	0.43	0.45	0.38	0.13	0.006 ⁺	0.26	0.21
95% CI	0.1–0.9	−0.008 to 0.2	−0.006 to 0.1				0.1–0.8	−0.3 to 1.0	−0.07 to 0.3			
Myocardial infarction												
Cohorts (patients), n	17 (15 007)	20 (8043)	20 (7688)									
Mean (SD)	0.2 (0.2)	0.1 (0.2)	0.2 (0.3)	0.14	1.00	0.22	−0.02	0.007	−0.07	0.75	0.92	0.18
95% CI	0.1–0.3	0.01–0.2	0.07–0.33				−0.2 to 0.1	−0.1 to 0.1	−0.2 to 0.03			
Hematoma												
Cohorts (patients), n	18 (9912)	36 (13 817)	21 (7407)									
Mean (SD)	1.6 (1.5)	1.1 (1.0)	0.7 (1.2)	0.21	0.04	0.18	0.01	0.78	0.39	0.98	0.002 ⁺	0.24
95% CI	0.9–2.3	0.8–1.4	0.2–1.2				−0.9 to 0.9	0.3–1.3	−0.3 to 1.0			
Lymphocele^d												
Cohorts (patients), n	34 (17 724)	28 (12 775)	28 (10 226)									
Mean (SD)	3.2 (3.3)	1.7 (1.2)	0.8 (1.3)	0.02 ⁺	0.0003 ⁺	0.009 ⁺	1.29	1.92	0.26	0.08	0.0003 ⁺	0.30
95% CI	2.1–4.3	1.3–2.1	0.3–1.3				−0.2 to 2.8	0.9–3.0	−0.3 to 0.7			
Anastomotic leakage^e												
Cohorts (patients), n	37 (15 544)	47 (14 192)	47 (19 925)									
Mean (SD)	10.0 (9.6)	3.7 (3.3)	3.5 (3.5)	<0.0001 ⁺	<0.0001 ⁺	0.78	6.33	5.18	0.39	<0.0001 ⁺	<0.0001 ⁺	0.61
95% CI	6.9–13.0	2.8–4.6	2.5–4.5				3.2–9.5	3.6–6.8	−1.1 to 1.9			
Fistula												
Cohorts (patients), n	22 (23 134)	42 (15 422)	16 (5173)									
Mean (SD)	0.07 (0.2)	0.3 (0.6)	0.03 (0.1)	0.03	0.42	0.007 ⁺	−0.27	0.04	0.13	0.01 ⁺	0.49	0.04
95% CI	−0.01 to 0.2	0.1–0.5	−0.02 to 0.08				−0.5 to −0.05	−0.06 to 0.1	0.01–0.3			
Bladder neck/Anastomotic stricture												
Cohorts (patients), n	25 (12 449)	32 (11 899)	36 (17 011)									
Mean (SD)	2.2 (3.6)	0.8 (1.1)	0.9 (0.8)	0.07	0.09	0.65	1.02	0.67	−0.48	0.04	0.31	0.08
95% CI	0.8–3.6	0.4–1.2	0.6–1.2				0.03–2.0	−0.6 to 2.0	−1.0 to 0.04			
Sepsis												
Cohorts (patients), n	13 (7432)	14 (6327)	15 (5920)									
Mean (SD)	0.2 (0.3)	0.2 (0.2)	0.1 (0.3)	1.00	0.39	0.30	0.07	0.11	0.13	0.36	0.17	0.03
95% CI	0.03–0.4	0.1–0.3	−0.05 to 0.25				−0.07 to 0.2	−0.04 to 0.3	0.01–0.3			
Wound infection												
Cohorts (patients), n	29 (12 968)	18 (7967)	23 (8495)									
Mean (SD)	2.8 (2.5)	0.7 (1.3)	0.7 (0.8)	0.0005 ⁺	0.0001 ⁺	1.00	1.35	1.61	0.40	0.01 ⁺	0.0009 ⁺	0.25
95% CI	1.9–3.7	0.1–1.3	0.4–1.0				0.3–2.4	0.7–2.6	−0.3 to 1.1			

RALP = robot-assisted laparoscopic radical prostatectomy; LRP = laparoscopic radical prostatectomy; ORP = open retropubic radical prostatectomy; SD = standard deviation; CI = confidence interval.

^a All perioperative outcomes adjusted for age, body mass index, preoperative Gleason score, preoperative prostate-specific antigen, and pathologic stage.

^b Nerve injuries include injuries to the obturator and ulnar nerves and reports of neurapraxia, nerve palsy, ulnar neuropathy, and axonal degeneration.

^c Bowel injuries include injuries to the duodenum, jejunum, ileum, cecum, colon, and sigmoid (all bowel except the rectum).

^d Lymphoceles were either symptomatic or asymptomatic, and rates were calculated using overall study size.

^e Anastomotic leakage includes urine leakage, urine extravasation, and urinoma; complication rates do not include transfusions because they are reported separately.

⁺ Significant at 5% level after adjusting for multiple comparisons (Hochberg correction).

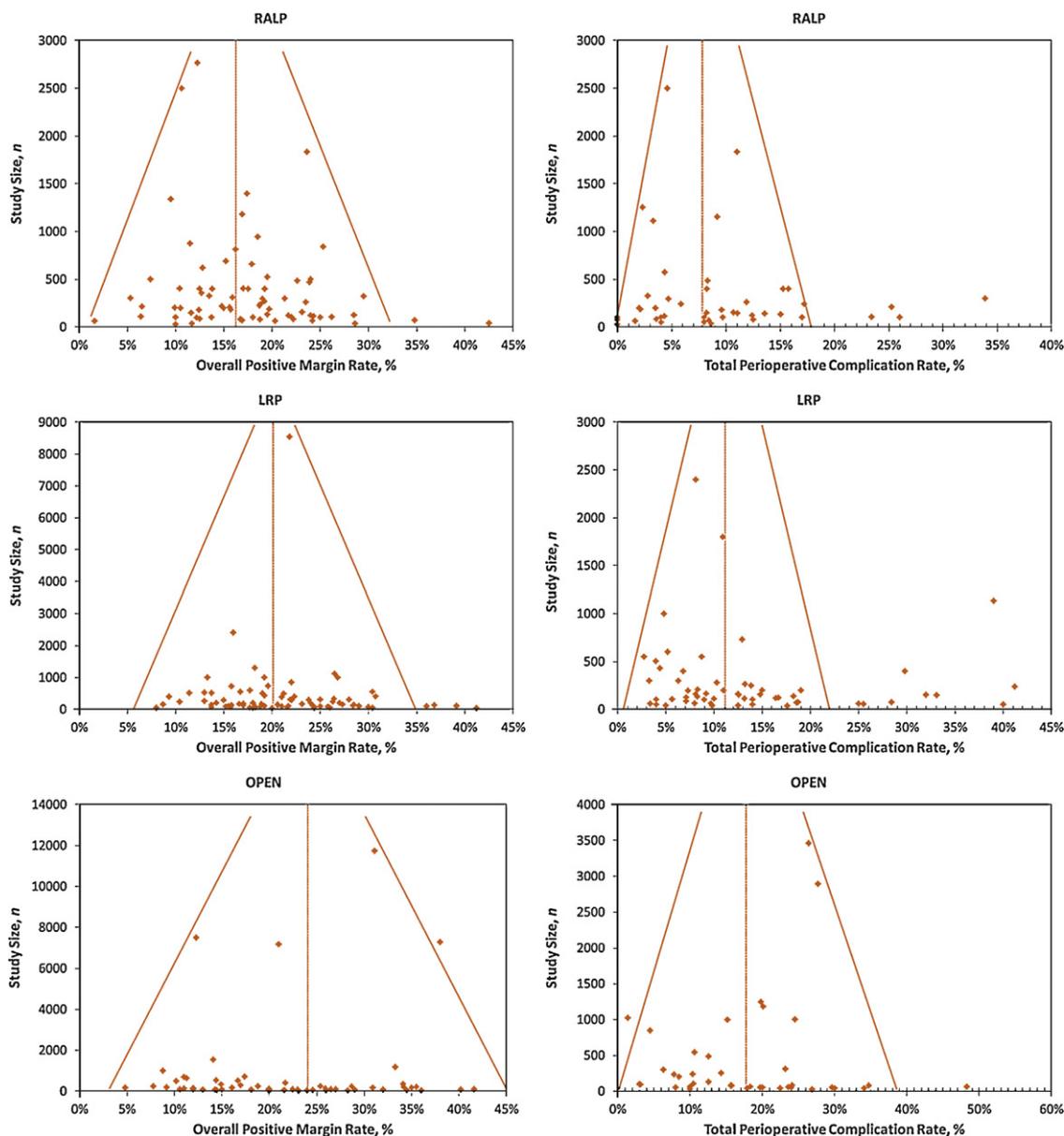


Fig. 4 – Funnel plot analysis. Scatter plots of treatment effect (overall positive margin rate or total perioperative complication rate) by study size are shown for robot-assisted laparoscopic radical prostatectomy (RALP), laparoscopic radical prostatectomy (LRP), and radical retropubic prostatectomy (Open). Vertical dotted lines represent the weighted averages. Solid lines are visual aids for identifying symmetry versus asymmetry, with a symmetric shape indicative of a “well-behaved” data set in which publication bias is unlikely.

adjustment and Hochberg correction (overall PSM $p = 0.002$; pT2 PSM $p = 0.01$). The rates for pT3 cancers (42.6% ORP, 39.7% LRP, and 37.2% RALP) were not significantly different after propensity adjustment and Hochberg correction. Total intraoperative complication rates were significantly higher for ORP (1.5%) versus RALP (0.4%) ($p < 0.0001$) and for LRP (1.6%) versus RALP (0.4%) ($p < 0.0001$). For total perioperative complication rates (17.9% ORP, 11.1% LRP, and 7.8% RALP), RALP versus ORP ($p < 0.0001$) and versus LRP ($p = 0.002$) were significant. Testing for heterogeneity with Q statistics yielded $p < 0.0001$ in all cases, and the percentage of total variance attributable to heterogeneity of outcomes between

studies as measured with the I^2 statistic varied from 59.7% to 98.7%. Funnel plot analysis demonstrated a lack of publication bias for overall PSM and an inconclusive finding for total perioperative complication rates (Fig. 4).

3.2. Secondary outcomes

The overall PSM rates did not significantly decrease with time for any cohorts (Table 5). The EBL and transfusion rates for ORP (745.3 ml; 16.5%) were higher than for LRP (377.5 ml; 4.7%) and RALP (188.0 ml; 1.8%). RALP had the shortest hospital stay, both in the US studies (1.4 d) and in

the non-US studies (4.0 d), with LRP intermediate (2.1 d US, 6.3 d non-US), and ORP having the longest length of stay (3.1 d US, 9.9 d non-US). All pairwise comparisons were statistically significant except for the LRP versus RALP transfusion rate comparison ($p = 0.07$) (Table 6). Conversion rates were low for both LRP (0.7%) and RALP (0.3%) and not significantly different between the modalities (Table 6).

Rates of mortality were low between groups (0.1% ORP, 0.04% LRP, and 0.04% RALP), with no significant differences after propensity score adjustments (Table 7). Although the unadjusted readmission rate for ORP (3.0%) was lower than RALP (3.5%), upon adjustment the readmission rate for ORP was estimated to be 4.2% higher than RALP ($p \leq 0.0001$), and the LRP rate (11.3%) was significantly higher than both the ORP and RALP rates ($p = 0.006$ and $p = 0.0003$, respectively). The reoperation rate for RALP (0.9%) was significantly lower than for LRP (1.9%; $p = 0.0001$). Vessel and bladder and bowel (not including rectal) injuries were reported infrequently or not at all for all three surgical modalities (<1%), with no significant differences after propensity score adjustments. Nerve injuries were significantly higher for LRP (2.0%) compared with RALP (0.4%; $p = 0.0006$), and ureteral injuries were statistically higher for ORP (1.5%) compared with RALP (0.1%; $p = 0.012$) and LRP (0.2%; $p = 0.02$). There was a significantly higher rectal injury rate for LRP (1.0%) versus RALP (0.3%; $p = 0.0002$) and versus ORP (0.5%; $p = 0.0002$). The rates of ileus, pulmonary embolism, myocardial infarction, bladder neck/anastomotic stricture, and sepsis were not significantly different between the groups. The rates of deep vein thrombosis were lowest for RALP (0.3%), intermediate for LRP (0.5%), and highest for ORP (1.0%) with all pairwise comparisons significant ($p = 0.02$, $p = 0.008$, and $p = 0.003$, respectively). Rates of pneumonia were significantly lower in the LRP group (0.1%) when compared with ORP (0.5%, 0.006) and were not significantly different than RALP rates (0.05%). RALP rates of hematoma (0.7%) and lymphocele (0.8%) were significantly lower than for ORP (hematoma: 1.6%, $p = 0.002$; lymphocele: 3.2%, $p = 0.0003$). Anastomotic leakage and wound infection rates were lower in both minimally invasive cohorts when compared with ORP. Finally, perioperative fistula rates were significantly higher for LRP (0.3%) than for ORP (0.07%; $p = 0.01$).

4. Conclusions

This study represents the largest compilation of radical prostatectomy patients to date, and it serves as a systematic review and meta-analysis of this vast body of literature. However, due to the lack of RCTs, differences in patient characteristics between surgical cohorts might explain differences in outcomes between treatment groups. These differences cannot be fully corrected with statistical methods. Additionally, unknown differences in certain attributes of the patients and physicians themselves and/or the administered treatments could contribute to the highly heterogeneous outcomes between studies. We thus caution readers to interpret the findings of this meta-analysis within the context of the considerations just described. Furthermore, due to the large numbers of patients included in this

meta-analysis, results that reach statistical significance may not necessarily be clinically meaningful.

Although there were significant differences between all three surgical approaches for the unadjusted overall and pT2 PSM rates, after propensity adjustment, the only significant differences were lower overall and pT2 PSM rates for RALP compared with LRP. This finding is not explained by differences in preoperative Gleason score or PSA because these parameters were included in the propensity adjustment. Interestingly, the crude difference in overall PSM rates for ORP and RALP of 8.0% (24.2% ORP; 16.2% RALP) was largely eliminated by the propensity adjustment. Given only slight differences between the groups in terms of preoperative Gleason score, much of this effect can be attributed to the higher preoperative PSA and pathologic stage averages of the ORP cohorts (7.5 ng/ml PSA, 28.6% pT3) compared with the RALP cohorts (6.3 ng/ml PSA, 20.1% pT3). The propensity-adjusted pT3 rates were not statistically different for all three surgical modalities after applying Hochberg corrections, which is not surprising because this is a function of the biology of the disease. A recent publication of 950 patients found higher PSM rates for RALP compared with ORP in contrast to our finding of equivalency. However, that study was a head-to-head single case series comparison of only one ORP and one robotic surgeon and not a comparison of a large number of surgeons as in this meta-analysis [24]. Other reviews have found lower PSM rates for RALP compared with LRP and/or ORP [9,25]. However, neither of those studies nor others included in this meta-analysis were able to account for potential inconsistencies in the pathologic processing of the specimen, such as whole mount versus standard processing; thus it is not clear how RALP's equivalence with ORP or superiority over LRP for PSM rates will translate into longer term oncologic results. However, a few recent reports have shown equivalent early (1–3 yr) [26,27] and midterm (5-yr) biochemical recurrence (BCR) rates for RALP, LRP, and ORP [28,29]. Specifically, one recent report on 2132 patients by Barocas et al. (2010) showed similar 3-yr BCR rates for ORP (83.5%) and RALP (84.0%; $p = 0.19$) [27], and another paper by Drouin et al. (2009) demonstrated equivalent oncologic outcomes at 5 yr between the three surgical modalities (5-yr BCR-free rates: 87.8% ORP, 88.1% LRP, and 89.6% RALP; $p = 0.93$) [29].

Total intraoperative complication rates and mortality rates were low for all surgical modalities, suggesting that radical prostatectomy is a safe procedure. The finding of reduced blood loss and transfusion rates in the LRP and RALP groups, with RALP causing the least bleeding, is commonly reported in the literature for MIS [3–6]. Our results also show that recovery as measured by hospital LOS was quickest for RALP, intermediate for LRP, and slowest for ORP. Along with lower readmission, reoperation, and total perioperative complication rates, this supports the notion of lower morbidity for RALP. Other studies have also confirmed a shorter overall convalescence period for RALP in terms of return to work, social activities, and activities of daily living [30,31]. It must be kept in mind that the complications reported in this meta-analysis were abstracted from articles that in the main (339 of 400; 85%) did not report

complications using a standardized method such as the Clavien classification system [32], and therefore it is possible that differential reporting of complications affected our findings. We did attempt to reduce bias using specific abstraction measures (Table 1) and can thus be reasonably confident that RALP is at least noninferior to LRP and ORP in terms of early complication rates.

Complications are also difficult to interpret without knowledge of comorbidities. However, 349 of 400 (87%) of the included articles did not mention comorbidity status at all, and only 11 of 400 articles (2.75%) reported comorbidity using the Charlson index. Although age was clinically similar between the surgical groups, thus suggesting that differences in comorbidities between cohorts might not have been large, readers are advised to consider that these differences might have existed and thus influenced complication rates. Another factor that could have influenced the results of this meta-analysis was differences in clinical stage between the surgical groups. Unfortunately, clinical stage was only reported consistent with the TNM system in 122 of 400 articles (30%). However, the inclusion of pathologic stage in this meta-analysis compensates to some extent for the lack of availability of clinical stage information. Route of access to the prostate during surgery can also affect complications. It was not possible to compare trans- and extraperitoneal approaches for MIS because only 13 of 307 articles (4.2%) separated their data based on route. In fact, many papers did not even mention which route was used (91 of 307; 29.6%). That said, most minimally invasive radical prostatectomies are performed transperitoneally, and thus the effect of different routes on various complication differences such as hematoma and lymphocele between the minimally invasive surgical modalities is likely to be modest.

Level of experience is a factor in determining outcomes, with largely comparable results published by high-volume surgeons in the field [27,33,34]. This meta-analysis does not provide evidence that one modality is superior to another among comparisons between high-volume surgeons. We were not able to do this comparison because many included studies did not state individual surgeon caseloads. Further evidence that learning curve could play a part in differential outcomes between treatment modalities is that a funnel plot analysis (Fig. 4) showed skewed complication outcomes, with smaller studies more often reporting higher complication rates, especially for LRP. It may be that included studies resulted in favorable results for RALP over LRP and ORP for some outcomes because the learning curve is shorter for RALP [20,35,36], and thus more so-called expert RALP surgeons were sampled in this meta-analysis than so-called expert LRP or ORP surgeons. Hence it may be that expert surgeons of any modality achieve similar results and that less experienced surgeons fare better with RALP for certain outcomes. Another possibility for our results is that known oncologic factors controlled for in this meta-analysis do not fully represent the biology of the disease. For example, lymph node status was not included in this meta-analysis because this information was often not available. Only 22 of 400 of the papers (5.5%) reported lymph node yield, a surrogate for the extent of lymphadenectomy. An additional 127 of 400 of the

papers (32%) reported on the number of patients who underwent lymphadenectomy, and the rest of the articles either gave no information at all (184 of 400; 46%), mentioned that lymphadenectomy was performed in patients who fulfilled specific criteria but did not give the number of patients (47 of 400; 12%), or just reported the number of positive lymph nodes (18 of 400; 4.5%). Therefore, readers are cautioned to interpret differences between surgical modalities in lymphatic-related complications such as lymphocele and thromboembolic disease with care.

Due to limiting the time frame of this study to 30 d postoperatively, this meta-analysis did not compare urinary continence or sexual potency outcomes. This is a limitation of the scope of this work, especially because these outcomes can be related to PSM rates, and thus these comparisons will be the subject of future work. Although Hu and colleagues [14] reported on these outcomes, interpretation of their results is difficult in the absence of validated questionnaires. A recent analysis by Alemozaffar et al. (2011) demonstrated relatively poor outcomes for radical prostatectomy in general with regard to intermediate-term (2-yr) erectile function, making comparisons between surgical modalities for this outcome yet more important [37]. Until all the preceding comparisons are made in a reliable and robust manner, it is not possible to recommend definitively one type of surgical approach over the other, but this meta-analysis is suggestive of at least equivalent PSM rates and improved perioperative morbidity profiles for RALP compared with LRP and ORP.

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Analysis and interpretation of data: Sooriakumaran, Bloch, Seshadri-Kreaden, Wiklund.

Drafting of the manuscript: Sooriakumaran, Hebert, Bloch, Seshadri-Kreaden.

Critical revision of the manuscript for important intellectual content: Tewari, Wiklund.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eururo.2012.02.029.

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