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[Intervention Review]

Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer

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ABSTRACT

Background

Prostate cancer is commonly diagnosed in men worldwide. Surgery, in the form of radical prostatectomy, is one of the main forms of treatment for men with localised prostate cancer. Prostatectomy has traditionally been performed as open surgery, typically via a retropubic approach. The advent of laparoscopic approaches, including robotic-assisted, provides a minimally invasive alternative to open radical prostatectomy (ORP).

Objectives

To assess the effects of laparoscopic radical prostatectomy or robotic-assisted radical prostatectomy compared to open radical prostatectomy in men with localised prostate cancer.

Search methods

We performed a comprehensive search using multiple databases (CENTRAL, MEDLINE, EMBASE) and abstract proceedings with no restrictions on the language of publication or publication status, up until 9 June 2017. We also searched bibliographies of included studies and conference proceedings.

Selection criteria

We included all randomised controlled trials (RCTs) with a direct comparison of laparoscopic radical prostatectomy (LRP) and robotic-assisted radical prostatectomy (RARP) to ORP, including pseudo-RCTs.

Data collection and analysis

Two review authors independently classified studies and abstracted data. The primary outcomes were prostate cancer-specific survival, urinary quality of life and sexual quality of life. Secondary outcomes were biochemical recurrence-free survival, overall survival, overall surgical complications, serious postoperative surgical complications, postoperative pain, hospital stay and blood transfusions. We performed statistical analyses using a random-effects model and assessed the quality of the evidence according to GRADE.

Main results

We included two unique studies with 446 randomised participants with clinically localised prostate cancer. The mean age, prostate volume, and prostate-specific antigen (PSA) of the participants were 61.3 years, 49.78 mL, and 7.09 ng/mL, respectively.

Primary outcomes

We found no study that addressed the outcome of prostate cancer-specific survival. Based on data from one trial, RARP likely results in little to no difference in urinary quality of life (MD -1.30, 95% CI -4.65 to 2.05) and sexual quality of life (MD 3.90, 95% CI -1.84 to 9.64). We rated the quality of evidence as moderate for both quality of life outcomes, downgrading for study limitations.

Secondary outcomes

We found no study that addressed the outcomes of biochemical recurrence-free survival or overall survival.

Based on one trial, RARP may result in little to no difference in overall surgical complications (RR 0.41, 95% CI 0.16 to 1.04) or serious postoperative complications (RR 0.16, 95% CI 0.02 to 1.32). We rated the quality of evidence as low for both surgical complications, downgrading for study limitations and imprecision.

Based on two studies, LRP or RARP may result in a small, possibly unimportant improvement in postoperative pain at one day (MD -1.05, 95% CI -1.42 to -0.68) and up to one week (MD -0.78, 95% CI -1.40 to -0.17). We rated the quality of evidence for both time-points as low, downgrading for study limitations and imprecision. Based on one study, RARP likely results in little to no difference in postoperative pain at 12 weeks (MD 0.01, 95% CI -0.32 to 0.34). We rated the quality of evidence as moderate, downgrading for study limitations.

Based on one study, RARP likely reduces the length of hospital stay (MD -1.72, 95% CI -2.19 to -1.25). We rated the quality of evidence as moderate, downgrading for study limitations.

Based on two study, LRP or RARP may reduce the frequency of blood transfusions (RR 0.24, 95% CI 0.12 to 0.46). Assuming a baseline risk for a blood transfusion to be 8.9%, LRP or RARP would result in 68 fewer blood transfusions per 1000 men (95% CI 78 fewer to 48 fewer). We rated the quality of evidence as low, downgrading for study limitations and indirectness.

We were unable to perform any of the prespecified secondary analyses based on the available evidence. All available outcome data were short-term and we were unable to account for surgeon volume or experience.

Authors' conclusions

There is no high-quality evidence to inform the comparative effectiveness of LRP or RARP compared to ORP for oncological outcomes. Urinary and sexual quality of life-related outcomes appear similar.

Overall and serious postoperative complication rates appear similar. The difference in postoperative pain may be minimal. Men undergoing LRP or RARP may have a shorter hospital stay and receive fewer blood transfusions. All available outcome data were short-term, and this study was unable to account for surgeon volume or experience.

PLAIN LANGUAGE SUMMARY

Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer

Review question

How does laparoscopic and robot-assisted laparoscopic surgery compare in the treatment of men with prostate cancer?

Background

Prostate cancer is a common cancer in men, often treated by surgical removal. Traditionally, surgeons used to make an incision on the lower abdomen to take the prostate. This procedure is called open radical prostatectomy (ORP). More recently, surgeons have started to use other ways to perform the same operation. Laparoscopic radical prostatectomy (LRP) allows surgeons to work inside the patient with long instruments and a tiny camera through small incisions. Laparoscopic surgery can be done with the use of a robotic device, which allows the surgeon to have a magnified, three-dimensional view and operate from a console, away from the patient. This procedure is called robotic-assisted radical prostatectomy (RARP). It is unclear whether the newer LRP and RARP approaches are better for patients.

Study characteristics

This review identified two randomised controlled trials of 446 men with prostate cancer, with an average age of approximately 60 years, that compared LRP or RARP to ORP.

Key results

We found no evidence as to how LRP or RARP compared to ORP in terms of reducing the risk of dying from prostate cancer, preventing the cancer from coming back or dying of any cause. Men's quality of life was likely similar related to their urinary and sexual function. There appears to be no differences in postoperative surgical complications. LRP or RARP may have a small possibly unimportant effect on postoperative pain at one day and up to one week. However, no difference between RARP and ORP was found at 12 weeks postoperatively. Men having LRP or RARP likely have a shorter hospital stay and may need fewer blood transfusions.

Quality of evidence

We found no trial evidence for any cancer outcome. The evidence for quality of life were moderate; that for overall and serious surgical complications were low quality. Postoperative pain were low (up to one week) and moderate (at 12 weeks) quality of evidence. The quality of evidence for hospital stay and blood transfusions were moderate and low, respectively. Collectively, the most outcomes were low to moderate quality of evidence. This means that our estimates are likely to be close to the truth but that there is a possibility that they may be different.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Laparoscopic radical prostatectomy and robotic-assisted laparoscopic radical prostatectomy compared to open radical prostatectomy for the treatment of localised prostate cancer

Laparoscopic radical prostatectomy and robotic-assisted laparoscopic radical prostatectomy compared to open radical prostatectomy for the treatment of localised prostate cancer

Participants: men with prostate cancer

Setting: single surgeon or single centre

Intervention: laparoscopic radical prostatectomy/robotic-assisted laparoscopic radical prostatectomy

Control: open radical prostatectomy

Outcomes	Nº of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with ORP	Risk difference with LRP/RARP
Prostate cancer-specific survival - not reported	-	-	-	-	-
Urinary quality of life (short-term) Assessed with: Expanded Prostate Cancer Index Composite ^a Follow-up: mean 3 months	248 (1 RCT)	⊕⊕⊕⊖ Moderate ^b	-	The mean score was 83.8	MD 1.3 lower (4.65 lower to 2.05 higher)
Sexual quality of life (short-term) Assessed with: Expanded Prostate Cancer Index Composite ^a Follow-up: mean 3 months	248 (1 RCT)	⊕⊕⊕⊖ Moderate ^b	-	The mean score was 35.0	MD 3.9 higher (1.84 lower to 9.64 higher)
Biochemical recurrence-free survival - not reported	-	-	-	-	-
Overall survival - not reported	-	-	-	-	-
Overall surgical complications (short-term) Follow-up: mean 3 months	308 (1 RCT)	⊕⊕⊖⊖ Low ^{b c}	RR 0.41 (0.16 to 1.04)	Study population 40 per 1000 Moderate	 23 fewer per 1000 (33 fewer to 2 more)

238 per 1000^d 140 fewer per 1000
(200 fewer to 10 more)

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **LRP:** Laparoscopic radical prostatectomy; **MD:** mean difference; **ORP:** open radical prostatectomy; **RCT:** randomised controlled trial; **RARP:** robotic-assisted laparoscopic radical prostatectomy; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

^a Expanded Prostate Cancer Index Composite contains five symptom domains (urinary incontinence, urinary irritative/obstructive, sexual, bowel, hormonal), scored from 0 (worst) to 100 (best).

^b Downgraded by one level for study limitation: unclear risk or high risk of one or more domains in included study or studies.

^c Downgraded by one level for imprecision: confidence interval crosses assumed threshold of clinically important difference.

^d Estimates for control event rates for surgical complications come from [Gandaglia 2014](#).

BACKGROUND

Description of the condition

Prostate cancer is a leading disease affecting men worldwide and accounting for 15% of cancers diagnosed in men (IARC 2012). In 2012 prostate cancer accounted for 14% of the total new cancers diagnosed worldwide, and 6% of total cancer deaths in men (Jemal 2011; Torre 2015). Incidence rates of prostate cancer vary by more than 25-fold worldwide, with the highest rates found in North America, Europe and Australasia (Jemal 2011). The age-standardised rate of prostate cancer incidence is higher in high-income countries than it is in low- and middle-income countries (56.2 per 100,000 versus 9.4 per 100,000) (Baade 2009). A similar trend is apparent with prostate cancer-specific mortality between high-income and low- and middle-income countries, with an age-standardised mortality rate of 13.5 per 100,000 and 5.2 per 100,000 respectively (Baade 2009).

Description of the intervention

Men diagnosed with localised prostate cancer have a variety of management options available, including radical prostatectomy (RP) (whether by open radical prostatectomy (ORP), laparoscopic approach (LRP), or robotic-assisted radical prostatectomy approach (RARP)). Other types of management include external beam radiation therapy, brachytherapy (including both high and low dose), active surveillance, watchful waiting, as well as investigational treatments, including whole-gland ablation therapy and focal-gland ablation therapy (Heidenreich 2011). Each respective treatment option aims to reduce the risk of prostate cancer-specific mortality, whilst minimising treatment-related morbidity and maintaining a good quality of life. Radical prostatectomy is recommended as a front-line treatment for men diagnosed with localised prostate cancer and with a life expectancy greater than 10 years (AUA 2013; EAU 2015; Heidenreich 2011).

The effectiveness of radical prostatectomy in treating localised prostate cancer has been evaluated in several recently published randomised controlled trials (RCTs) (Bill-Axelson 2014; Hamdy 2016; Wilt 2012). A 2014 RCT compared radical prostatectomy to watchful waiting with a median follow-up period of 23.2 years (Bill-Axelson 2014). In this study, radical prostatectomy significantly reduced prostate cancer-specific mortality when compared to watchful waiting (RR 0.56, 95% CI 0.41 to 0.77), with an overall number needed to treat for an additional beneficial outcome of 8 (Bill-Axelson 2014). The benefit of surgery was largest in men aged below 65 years, and in those with a low- and moderate-risk prostate cancer (Bill-Axelson 2014). It should also be noted that the participants in this study were men whose cancers were identified through symptoms, rather than widespread prostate-specific antigen (PSA) testing. The study by Wilt 2012 examined the effectiveness of surgery versus observation for men with localised prostate cancer, detected via PSA testing. A follow-up period of 10 years identified no significant difference in prostate cancer mortality between the two interventions (HR 0.88, 95% CI 0.71 to 1.08). Radical prostatectomy was associated with a reduction in all-cause mortality for men with a PSA value greater than 10 ng/mL and those with intermediate and high-risk tumours. The most recent study by Hamdy 2016 compared active monitoring, radical prostatectomy, and external-beam radiotherapy for the treatment of clinically localised prostate cancer. Prostate cancer mortality

measured at 10-year median follow-up identified no significant difference between the treatment arms.

The late 1990s saw the introduction of minimally invasive techniques for performing RP with the aim of reducing postoperative morbidity and allowing faster recovery when compared to traditional ORP (Schuessler 1997). Initially, surgeons adopting the LRP (also known as minimally invasive radical prostatectomy) approach needed to overcome significant technical challenges and a significant learning curve (Ficcara 2007). The introduction of robotic assistance using the da Vinci® surgical system (Intuitive Surgical 2011) led to the development of RARP in the early 2000s (Binder 2001), and offered technical innovations (3D visualisation, articulated instruments, tremor filtration) which addressed some of the technical limitations of LRP.

How the intervention might work

An initial feasibility report into the use of LRP concluded that it was a feasible procedure, but benefits with regard to tumour removal, continence, erectile function, and length of stay were negligible compared to open radical prostatectomy (Schuessler 1997). Other studies have been reported, since this initial feasibility study that standardised the techniques used for LRP (Guillonneau 1999). The robotic systems were introduced to provide surgeons with the ability to reduce the difficulty in performing LRPs (Hemel 2002). The first RARP was performed in 2000, and has since been widely adopted internationally for urological, gynaecological and cardiothoracic surgery (Binder 2001; Brandina 2009; Measo 2010; Uberti 2010).

Why it is important to do this review

Since the introduction of RARP a number of advantages and limitations have been reported in comparison to ORP and LRP. Such comparisons centre on the amount of blood loss during surgery, hospital length of stay, surgical margin status, urinary continence, erectile function, and other quality-of-life indicators (Parsons 2008).

OBJECTIVES

To assess the effects of laparoscopic radical prostatectomy or robotic-assisted radical prostatectomy compared to open radical prostatectomy in men with localised prostate cancer.

METHODS

Criteria for considering studies for this review

Types of studies

All forms of RCTs were eligible for inclusion in this review, including pseudo-RCTs.

Types of participants

Adult men, 18 years of age or older, of any ethnicity, diagnosed with clinically localised prostate cancer were eligible for inclusion in this review. Men with a diagnosis of prostate cancer, who had been treated previously for prostate cancer with any intervention (e.g. surgery, brachytherapy, complementary medicines) were not eligible for inclusion.

Types of interventions

We planned to investigate the following comparisons of experimental intervention versus comparator intervention.

Experimental interventions

- Laparoscopic radical prostatectomy (LRP) or robotic-assisted radical prostatectomy (RARP)

Comparator interventions

- Open radical prostatectomy (ORP)

Comparisons

- LRP or RARP versus ORP

Types of outcome measures

We did not use the measurement of the outcomes assessed in this review as an eligibility criterion.

Primary outcomes

- Prostate cancer-specific survival
- Urinary quality of life
- Sexual quality of life

Secondary outcomes

- Biochemical recurrence-free survival
- Overall survival
- Overall surgical complications
- Serious postoperative complications
- Postoperative pain
- Hospital stay
- Blood transfusions

Method and timing of outcome measurement

We used minimal clinically important difference (MCID) for the review outcomes to rate overall quality of the evidence in the 'Summary of findings' table (Jaeschke 1989).

Prostate cancer-specific survival

- Measured as the date of randomisation to the date of death due to prostate cancer (Mariotto 2014).
- We did not find any published information on MCID for prostate cancer-specific survival.

Urinary quality of life

- Mean change assessed with a validated questionnaire such as urinary domain of Expanded Prostate Cancer Index Composite (EPIC; Chang 2011; Szymanski 2000; Wei 2000).
- We considered the MCID in the urinary quality of life domain of EPIC-short form (EPIC-26) to be 6 points (Skolarus 2015).

Sexual quality of life

- Mean change assessed with validated questionnaires such as sexual domain of EPIC (Chang 2011; Szymanski 2000; Wei 2000), erectile function (EF) domain of international index of erectile function (IIEF; Rosen 1997), or total score of IIEF-5 (Rosen 1997).

- We used the MCID of sexual domain of EPIC-26 of 10 points (Skolarus 2015). We considered the MCID in the EF domain score of IIEF of four points (Rosen 2011). We also considered improvement of IIEF-5 of over five points as MCID (Spaliviero 2010).

Biochemical recurrence-free survival

- Measured as the date of randomisation to the date of biochemical recurrence which was defined as a PSA value 0.2 ng/mL after RP and confirmed by at least two consecutive measurements (AUA 2013; EAU 2015).
- We did not find any published information on MCID for biochemical recurrence-free survival.

Overall survival

- Measured as the date of randomisation to the date of death due to any cause (Mariotto 2014).
- We did not find any published information on MCID for overall survival.

Overall surgical complications

- All postoperative surgical complications such as postoperative haemorrhage, fever, pain, wound infection or dehiscence, hospitalisation, or life-threatening complications requiring treatment.
- While no threshold was established for the major and minor adverse events, we considered the MCID as relative risk reduction (RRR) of at least 25% (Guyatt 2011).

Serious surgical complications

- Such as postoperative haemorrhage requiring admission or intervention, or life-threatening complications.
- We used the Clavien-Dindo classification system (Dindo 2004) to assess the complications and categorized grade III, IV and V complications as serious surgical complications. We considered the MCID as RRR of at least 25% (Guyatt 2011).

Postoperative pain

- Assessed with validated questionnaires such as visual analogue scale (VAS) score (DeLoach 1998).
- We considered the MCID to be 10.0 mm on a 100 mm VAS scale to assess efficacy and comparative effectiveness (Kelly 2001).

Hospital stay

- Measured in days from admission to discharge.
- No threshold was established for the hospital stay. We used a MCID of one day to assess efficacy and comparative effectiveness.

Blood transfusions

- Measured as frequencies after surgery.
- No threshold was established for the blood transfusion. We considered the MCID in the blood transfusions as a RRR of at least a 25% (Guyatt 2011).

We planned to assess outcomes as short-term (one year or less post-intervention) and long-term (more than one year post-intervention) for prostate cancer-specific survival, urinary quality of life, sexual quality of life, biochemical recurrence-free survival,

overall survival. We assessed overall surgical complications, serious surgical complications, postoperative pain, hospital stay, and blood transfusions as short-term only.

Main outcomes for 'Summary of findings' table

Based on our published protocol, we have presented a 'Summary of findings' table reporting the following outcomes, listed according to priority.

- Prostate cancer-specific survival
- Urinary quality of life
- Sexual quality of life
- Biochemical recurrence-free survival
- Overall survival
- Overall postoperative complications

Search methods for identification of studies

We performed a comprehensive search with no restrictions on the language of publication or publication status. We initially ran searches on 13 December 2016 followed by an updated search on 9 June 2017.

Electronic searches

We conducted electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, issue 6) in the Cochrane Library (for the search strategy, see [Appendix 1](#)), MEDLINE Ovid (1946 to 9 June 2017) ([Appendix 2](#)) and EMBASE Ovid (1974 to June 2017) ([Appendix 3](#)).

Searching other resources

We searched bibliographies of identified studies for additional studies and contacted authors of identified studies for knowledge of any published or unpublished studies, including new, additional studies, or works in progress. We handsearched relevant conference proceedings for three years, from 2015 to 2017, for unpublished studies from annual meetings of the American Urological Association (EUA) and the European Association of Urology (EAU).

Data collection and analysis

Selection of studies

Two review authors (DI and CA) independently screened the titles and abstracts of all articles identified through the search strategy. Two review authors (DI and CA) investigated all potentially relevant records as full text, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). We documented reasons for exclusion of studies that may have reasonably been expected to be included in the review in a [Characteristics of excluded studies](#) table. We presented an adapted PRISMA flow diagram showing the process of study selection ([Liberati 2009](#)).

Data extraction and management

We developed a dedicated data abstraction form that we pilot tested ahead of time.

For studies that fulfilled inclusion criteria, two review authors (DI and CA) independently abstracted the following information, which we provided in the [Characteristics of included studies](#) table:

- Study design
- Study dates (if dates were not available then this was reported as such)
- Study settings and country
- Participant inclusion and exclusion criteria
- Participant details, baseline demographics (e.g. age, prostate-specific antigen, tumour stage, and Gleason score)
- The number of participants by study and by study arm
- Details of relevant experimental intervention (e.g. LRP and RARP) and ORP
- Definitions of relevant outcomes, and method (e.g. type of instrument such as EPIC and IIEF) and timing of outcome measurement (e.g. in months) as well as any relevant subgroups (e.g. based on type of interventions and prostate risk classification)
- Study funding sources
- Declarations of interest by primary investigators

We extracted outcomes data relevant to this Cochrane Review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we attempted to obtain numbers of events and totals for population of a 2 x 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we attempted to obtain means and standard deviations or data necessary to calculate this information.

We planned to provide information, including trial identifier, about potentially relevant ongoing studies in the table Characteristics of ongoing studies, however we did not identify any ongoing studies.

We attempted to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary study, we maximised yield of information by mapping all publications to unique studies and collating all available data. We used the most complete data-set aggregated across all known publications. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (DI and CA) independently conducted a 'Risk of bias' assessment using the Cochrane 'Risk of bias' assessment tool ([Higgins 2011b](#)) on all included trials. Each review author independently assessed the following domains and graded each criterion as 'low', 'unclear', or 'high' risk of bias.

Assessment of risk of bias in RCTs

We assessed risk of bias using Cochrane's 'Risk of bias' assessment tool ([Higgins 2011b](#)). We assessed the following domains:

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)

- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other sources of bias

For selection bias (random sequence generation and allocation concealment), we evaluated risk of bias at a trial level.

For performance bias (blinding of participants and personnel), we evaluated the risk of bias separately for each outcome. We considered all outcomes similarly susceptible to performance bias. We considered all outcomes were susceptible and assessed them in one group.

For detection bias (blinding of outcome assessment), we grouped outcomes as susceptible to detection bias (subjective) or not susceptible to detection bias (objective).

- Susceptible/subjective: prostate cancer-specific survival, urinary quality of life, sexual quality of life, biochemical recurrence-free survival, overall surgical complications, and serious postoperative complications
- Not susceptible/objective: overall survival, postoperative pain, hospital stay, blood transfusions

We assessed attrition bias (incomplete outcome data) and reporting bias (selective reporting) on a per-outcome basis but sought to create groups of outcomes based on similar reporting characteristics.

- Oncological outcomes: prostate cancer-specific survival, biochemical recurrence-free survival, overall survival
- Quality-of-life outcomes: urinary quality of life, sexual quality of life
- Overall surgical complications, serious postoperative complications, postoperative pain, hospital stay, and blood transfusions

Measures of treatment effect

We performed statistical analyses according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We expressed dichotomous outcomes as risk ratio (RR) with 95% confidence intervals (CIs) and reported continuous outcome measures as mean difference (MD) with 95% CIs. For measures recorded at different time points, we used the longest point after randomisation for any comparative analysis between studies. We planned to express time-to-event data as hazard ratios (HRs) with 95% CIs. However, we did not find any published time-to-event data.

Unit of analysis issues

We included simple, parallel-group design RCTs in this review, with participants randomised to one of two intervention groups (ORP or LRP/ RARP). We obtained a single unit of measurement for each individual in the study.

Dealing with missing data

We obtained missing data from study authors, if feasible, and performed intention-to-treat analyses if data were available; we otherwise performed available case analyses. We investigated attrition rates, (e.g. drop-outs, losses to follow-up and withdrawals)

and critically appraised issues of missing data. We did not impute missing data.

Assessment of heterogeneity

We assessed heterogeneity statistically with the I^2 statistic (Higgins 2003), and graphically via graphical interpretation of forest plots. An I^2 statistic above 75% was considered to be an indicator of considerable heterogeneity (Deeks 2011).

Assessment of reporting biases

We attempted to obtain study protocols to assess for selective outcome reporting.

Data synthesis

We summarised data using a random-effects model. We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). For dichotomous outcomes, we used the Mantel-Haenszel method; for continuous outcomes, we used the inverse variance method. We used Review Manager 5 (RevMan 5) software to perform analyses (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We planned to conduct the following subgroup analyses.

- LRP versus RARP
- Pathological tumour stage (i.e. T2 versus T3 disease)

These subgroup analyses were based on the following observations.

- RARP and LRP are different procedures. LRP has been reported to require a high level of surgical skills and has a steeper learning curve (Ficcara 2007; Hemel 2002). RARP requires the use of a robotic-assisted device that is associated with high acquisition and maintenance costs (Binder 2001).
- Higher local tumour stage represents a higher risks for positive surgical margins and prompts a different surgical approach, which may impact on urinary quality of life and sexual quality of life (AUA 2013; EAU 2015). It is unclear whether the results differ by LRP/RARP versus ORP.

We planned to perform subgroup analyses limited to the primary outcomes only.

Sensitivity analysis

We planned to perform sensitivity analyses limited to the primary outcomes in order to explore the influence of the following factor (when applicable) on effect sizes.

- Restricting the analysis by taking into account risk of bias by excluding studies at 'high risk' or 'unclear risk'.

RESULTS

Description of studies

Results of the search

A search of all electronic databases returned 85 citations ([Figure 1](#)) with no further records identified through other sources. After

removal of duplicates, we found 49 citations eligible for screening against the inclusion criteria for this review. We excluded a total of 46 records based on reading the title and abstract. We screened three full-text articles, of which one was excluded ([Magheli 2014](#)). We assessed two studies as eligible for inclusion in this review ([Guazzoni 2006](#); [Yaxley 2016](#)). The flow of literature through the assessment process is shown in the PRISMA flowchart ([Figure 1](#)) ([Liberati 2009](#)).

Figure 1. Study flow diagram

Included studies

A detailed description of the baseline characteristics and participants of the included studies is presented elsewhere (see [Characteristics of included studies](#); [Table 1](#); [Table 2](#)).

Source of data

The electronic database search identified both of the included trials. We contacted all trial authors of the included trials to identify any further information on study methodology and results, and received reply from [Yaxley 2016](#).

Study design and settings

The two included studies were parallel-RCTs. [Yaxley 2016](#) used block randomisation with age stratification (40–49 years, 50–59 years, 60–69 years) and reported to be blinded for study investigators involved in data analysis but participants were telephoned about their designated surgical procedure. [Guazzoni 2006](#) randomised participants using a computer-generated table. [Guazzoni 2006](#), a single-surgeon study, was done in Milan, Italy. [Yaxley 2016](#), a single-centre study, was performed in Queensland, Australia. One study was performed from 2010 to 2014 ([Yaxley 2016](#)), but [Guazzoni 2006](#) did not state the study duration.

Participants

This review includes 446 randomised participants in total (LRP or RARP 223, ORP 223), of whom a total of 428 subsequently finished for the intervention and control groups (LRP or RARP 217, ORP 211). The mean age, prostate volume, and PSA of the participants were 61.3 years, 49.78 mL, and 7.09 ng/mL, respectively. Both the studies included participants with clinically localised prostate cancer. However, [Yaxley 2016](#) included participants with a Gleason score of more than 8. In addition, [Yaxley 2016](#) included participants who are able to read and speak English. Men with PSA greater than 20 ng/mL were excluded from both of the included studies. [Guazzoni 2006](#) limited the prostate volume to less than 60 mL.

Interventions and comparators

[Guazzoni 2006](#) compared LRP to ORP. LRP was performed via the trans-peritoneal route according to the Montsouris technique ([Guillonneau 2002](#)), and ORP was performed using the anatomic technique described by [Walsh 2000](#). Single surgeons performed all procedures. [Yaxley 2016](#) compared RARP to ORP. To reduce heterogeneity, each surgical procedure was done by the same surgeon. Pelvic lymph node dissection was performed in participants with a serum PSA greater than 10 ng/mL, or Gleason score more than 7 in both studies. [Guazzoni 2006](#) and [Yaxley 2016](#), used limited and standardised templates respectively. Nerve-sparing procedures were undertaken based on preoperative parameters including clinical staging in both included studies. Pain control was done based on analgesic protocol in [Guazzoni 2006](#), but epidural or spinal anaesthesia was not used routinely in [Yaxley 2016](#).

Outcomes

[Guazzoni 2006](#) compared LRP to ORP and followed up for six days postoperatively, with reported outcomes including length of stay, success rate in nerve sparing, blood loss and quality of life (as measured by pain). [Yaxley 2016](#) reported non-oncological participant outcomes including, postoperative complications, pain, physical and mental functioning, fatigue, preference-based utility scores, bowel function, cancer-specific distress, psychological distress, and time to return to work comparing RARP to ORP. Outcomes were measured preoperatively and at six and 12 weeks postoperatively. They also planned to report oncological outcomes including positive surgical margins and biochemical recurrence at 24 months postoperatively.

Excluded studies

We excluded one study due to not being a RCT after evaluation of the full publication ([Magheli 2014](#)) see [Characteristics of excluded studies](#).

Risk of bias in included studies

See [Figure 2](#), [Figure 3](#), and the [Characteristics of included studies](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Figure 2. (Continued)

	Random seq	Allocation c	Blinding of I	Blinding of (	Blinding of (	Incomplete i	Incomplete i	Incomplete i	Incomplete i	Selective ref	Selective ref	Selective ref	Other bias
Guazzoni 2006	+	?	-	?	+	?	?	+	+	?	?	?	?
Yaxley 2016	+	?	-	+	+	+	-	+	-	+	+	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Allocation

Random sequence generation

Both studies reported an adequate method of sequence generation and we rated them at low risk of bias.

Allocation concealment

We rated both included studies as unclear risk of bias due to lack of information.

Blinding

Blinding of participants and personnel

We judged both included studies as high risk of bias.

Blinding of outcome assessor

- Susceptible/subjective outcomes (prostate cancer-specific survival, urinary quality of life, sexual quality of life, biochemical recurrence-free survival, overall surgical complications, serious postoperative complications): we rated one study as low risk of bias (Yaxley 2016), but the other as unclear risk of bias (Guazzoni 2006).
- Not susceptible/objective outcomes (overall survival, postoperative pain, hospital stay, blood transfusions): we judged both included studies as low risk of bias.

Incomplete outcome data

- Oncological outcomes (prostate cancer specific survival, biochemical recurrence-free survival, overall survival): we rated one study as low risk of bias (Yaxley 2016), but the other as unclear risk of bias (Guazzoni 2006).
- Quality-of-life outcomes (urinary quality of life, sexual quality of life): we rated one study as high risk of bias (Yaxley 2016), but the other as unclear risk of bias (Guazzoni 2006).
- Overall surgical complications, serious postoperative complications, hospital stay, and blood transfusions: we judged both included studies as low risk of bias.
- Postoperative pain: we rated one study as low risk of bias (Guazzoni 2006), but the other as high risk of bias (Yaxley 2016).

Selective reporting

For all outcomes, we rated one study, which had a published protocol, as low risk of bias (Yaxley 2016), but the other as unclear risk of bias (Guazzoni 2006).

Other potential sources of bias

We rated one study as low risk of bias (Yaxley 2016), but the other as unclear risk of bias due to statistically significant differences in the nerve-sparing procedures between the interventions, which may have affected the prognosis (Guazzoni 2006).

Effects of interventions

See: [Summary of findings for the main comparison Laparoscopic radical prostatectomy and robotic-assisted laparoscopic radical prostatectomy compared to open radical prostatectomy for the treatment of localised prostate cancer](#)

Laparoscopic or robotic-assisted versus open radical prostatectomy

Primary Outcomes

Prostate cancer-specific survival

Neither of the two trials reported this outcome.

Urinary quality of life

One included study (Yaxley 2016) reported data for this outcome for 248 participants (RARP 129, ORP 119). RARP likely results in little to no difference in urinary quality of life (MD -1.30, 95% CI -4.65 to 2.05). We rated the quality of the evidence as moderate according to GRADE, downgrading for study limitations.

Sexual quality of life

One included study (Yaxley 2016) reported data for this outcome for 248 participants (RARP 129, ORP 119). RARP likely results in little to no difference in sexual quality of life (MD 3.90, 95% CI -1.84 to 9.64). We rated the quality of the evidence as moderate according to GRADE, downgrading for study limitation.

Secondary Outcomes

Biochemical recurrence-free survival

Neither of the two trials included in this review reported this outcome.

Overall survival

Neither of the two trials included in this review reported this outcome.

Overall surgical complications

One included study (Yaxley 2016) reported data for this outcome for 308 participants (RARP 157, ORP 151). RARP likely results in little to no difference in postoperative surgical complications (RR 0.41, 95% CI 0.16 to 1.04). We rated the quality of the evidence as low according to GRADE, downgrading for study limitations and imprecision.

Serious postoperative complications

One included study (Yaxley 2016) reported data for this outcome for 308 participants (RARP 157, ORP 151). RARP likely results in little to no difference in serious surgical complications (RR 0.16, 95% CI 0.02 to 1.32). We rated the quality of the evidence as low according to GRADE, downgrading for study limitations and imprecision.

Postoperative pain

We included two studies with 428 participants (LRP or RARP 217, ORP 211) and 370 participants (LRP or RARP 190, ORP 180) for postoperative follow-up at one day and up to one week (Guazzoni 2006; Yaxley 2016). LRP or RARP may result in a small effect that may not be an important improvement in postoperative pain (at one day: MD -1.05, 95% CI -1.42 to -0.68), (up to one week: MD -0.78,

95% CI -1.40 to -0.17). We rated the quality of the evidence as low for both according to GRADE, downgrading for study limitations and imprecision. We included only one study with 250 participants (RARP 130, ORP 120) with postoperative 12-week follow-up (Yaxley 2016). RARP likely results in little to no difference in postoperative pain at 12 weeks (MD 0.01, 95% CI -0.32 to 0.34). We rated the quality of the evidence as moderate according to GRADE, downgrading for study limitations.

Hospital stay

Only one included study (Yaxley 2016) reported data for this outcome for 308 participants (RARP 157, ORP 151). RARP likely reduces the length of hospital stay (MD -1.72, 95% CI -2.19 to -1.25). We rated the quality of the evidence as moderate according to GRADE, downgrading for study limitations.

Blood transfusions

Both the included studies (Guazzoni 2006; Yaxley 2016) reported data for this outcome for 428 participants (LRP or RARP 217, ORP 211). LRP or RARP may reduce the frequency of blood transfusions postoperatively (RR 0.24, 95% CI 0.12 to 0.46). Assuming a baseline risk of blood transfusion to be 8.9% (Gandaglia 2014), LRP or RARP would result in 68 fewer blood transfusions per 1000 men (95% CI 78 fewer to 48 fewer). We rated the quality of the evidence as low according to GRADE, downgrading for study limitations and indirectness. We downgraded for indirectness since all participants in the Guazzoni 2006 study banked two units of autologous blood, which may have increased transfusion requirements. This study contributed 90% of the weight of the analysis.

Subgroup analysis

We did not perform a subgroup analysis because there were no relevant data.

Sensitivity analysis

We did not perform a sensitivity and subgroup analysis due to a paucity of included studies.

DISCUSSION

Summary of main results

A central finding of this review was the lack of high quality evidence to support equivalence or superiority of oncological outcomes, in particular prostate cancer-specific survival, but also biochemical and recurrence-free survival.

RARP likely results in little to no difference in urinary and sexual quality of life. RARP appears similar with regards to overall surgical complications and serious postoperative complications.

LRP or RARP may have a small unimportant effect on postoperative pain up to one week but RARP appears similar at 12 weeks. RARP likely reduces the length of hospital stay and LRP or RARP may reduce the frequency of blood transfusions.

Overall completeness and applicability of evidence

- This review is based on only two randomised controlled trials with relatively small sample sizes and event rates conducted at tertiary care centres with expert surgeons (Guazzoni 2006; Yaxley 2016). This narrow evidence base stands in marked contrast to

the widespread use of RARP in many countries, in particular in the USA (Stitzenberg 2012).

- A major limitation of the evidence drawn from this review is the lack of high-quality evidence to inform the comparison of any oncological outcomes, resulting in major uncertainty. An understanding of these outcomes therefore has to come from observational studies that were outside the scope of this review and are likely to only yield low-quality evidence (Schunemann 2013).
- All outcome data, including that on quality of life, was short-term. Given that prostate cancer survivorship, which includes dealing with the potential adverse events of radical surgery, such as urinary incontinence and erectile dysfunction commonly extends over decades, the information provided appears insufficient to guide clinical practice. Longer term, well-controlled studies are needed.
- One of the central challenges of assessing surgical innovation lies in the need to account for ongoing evolution of the procedure or device, or both, being used, as well as accounting for the surgical learning curve (Dahm 2014; Dahm 2016). It is well recognised that surgical outcomes are dependent on surgeons' and centres' volume and experience. This review is unable to account for these differences, which may be more important factors than the surgical approach.
- While RARP (and less so today, LRP) has tremendous appeal to surgeons, due, among other things, to magnification of the operative field and 3-D imaging, device acquisition and maintenance/service are costly. However, an assessment of the cost-effectiveness of LRP/RARP was outside the scope of this review.

Quality of the evidence

We consistently downgraded the quality of the evidence for all outcomes to moderate, except for postoperative surgical complications, postoperative pain, and blood transfusions. The main issues that lowered our confidence in the estimates of effect were study limitations, specifically unclear allocation concealment (selection bias) and the lack of blinding (performance and detection bias). For postoperative surgical complications and postoperative pain at one day and up to one week, we rated the quality of the evidence as low due to study limitations and imprecision (confidence interval that crosses predefined MCIDs). We downgraded the quality of the evidence for blood transfusions as low due to study limitations and indirectness (different standard of care; autologous transfusion).

Potential biases in the review process

This review employed a comprehensive search strategy of multiple data sources to search for RCTs irrespective of publication status and language. Despite this, there is a possibility that we may have missed published studies in a language other than English, published in non-indexed journals or not published at all.

Agreements and disagreements with other studies or reviews

A systematic search of the literature identified no published systematic reviews of RCTs, clinical practice guidelines reporting

findings, or recommendations, with respect to the use of ORP versus LRP in the treatment of localised prostate cancer. Several systematic reviews of observational studies have been completed, and generally support the findings reported in this systematic review (Bolenz 2014; De Carlo 2014; Ficcaro 2007; Heer 2011; Moran 2013; Novara 2012). Previous systematic review evidence from observational studies has demonstrated lower rates of blood loss, blood transfusion, postoperative complications, pain and length of hospital stay for the LRP/RARP (De Carlo 2014; Heer 2011; Novara 2012; Tooher 2006). Conversely, urinary and sexual quality of life have been reported in observational studies to be significantly better in men receiving RARP compared to ORP (Moran 2013). However, none of these studies used GRADE to assess the quality of evidence. Findings from our systematic review support previous findings that have reported lower rates of blood transfusion, postoperative pain, and length of hospital stay in LRP/RARP groups (De Carlo 2014; Moran 2013; Tooher 2006).

AUTHORS' CONCLUSIONS

Implications for practice

People should be informed about the lack of high-quality evidence from RCTs to inform prostate cancer-specific survival and other oncological outcomes. Given that the indication for radical surgery is motivated by men's concern about prostate cancer-related morbidity and mortality, this information appears very important. While LRP or RARP were not associated with meaningful impact on quality of life, postoperative surgical complications and postoperative pain, those offer advantages when it comes to length of hospital stay and blood transfusions.

Implications for research

Evidence from previous systematic reviews of non-RCTs have uniformly concluded that the quality of the evidence base in observational studies is low (Kang 2010; Moran 2013). Whilst there is an urgent need to raise methodological standards for clinical research on new urologic procedures and devices (Kang 2010), the reality of creating future RCTs may be restricted by the challenges of conducting controlled trials of surgical interventions. Until such time, extended follow-up from the Yaxley 2016 study will hopefully inform our understanding of longer-term outcomes. Better understanding of the impact of risk of LRP/RARP on oncological outcomes is urgently needed.

Neither of the studies included in this systematic review controlled for surgeon or medical centre experience or expertise. Such factors may significantly confound measured outcomes including length of hospital stay, postoperative pain, functional and oncological outcomes, as well as potential adverse events. Further research in this context is required to better understand the potential confounding effects of these factors.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Guazzoni 2006

Methods	<p>Study design: prospective, RCT</p> <p>Setting/country: single surgeon/Italy</p> <p>Dates when study was conducted: not reported</p>
Participants	<p>Inclusion criteria: men aged < 70 years, clinically organ-confined disease (cT1 - cT2), total serum PSA < 20 ng/mL, Gleason score ≤ 7</p> <p>Exclusion criteria: men with previous hormone blockade therapy or any previous prostatic, bladder neck, urethral or pelvic surgery and total prostate volume ≥ 60 mL</p> <p>Total number of participants randomly assigned: 120</p> <p>Group A (LRP)</p> <ul style="list-style-type: none"> • Number of all participants randomly assigned: 60 • Age (years): 62.29 ± 8.2 • Prostate volume (mL): 39.1 ± 18.0 • PSA (ng/mL): 6.9 ± 2.9 • Pathologic stage: T2 (75%), T3 (25%), surgical margin positive (26%) • Pathologic Gleason score: not reported <p>Group B (ORP)</p> <ul style="list-style-type: none"> • Number of all participants randomly assigned: 60 • Age (years): 62.9 ± 7.4 • Prostate volume (mL): 40.0 ± 13.0 • PSA (ng/mL): 6.5 ± 3.0 • Pathologic stage: T2 (73.3%), T3 (26.6%), surgical margin positive (21.6%) • Pathologic Gleason score: not reported
Interventions	<p>Group A: LRP</p> <p>Group B: ORP</p> <p>Blood banking: all participants band 2 U of autologous blood (400 mL each)</p> <p>Surgeon: all procedures in both groups were performed by a senior urologist (G.G.) who had been performing RRP for the previous 15 years and had started his general laparoscopic experience 12 years before the study and, in particular, LRPs in 1999 (i.e. > 150 procedures to date)</p> <p>Surgical procedure: LRP was performed via the trans-peritoneal route according to the Montsouris technique (Guilonneau 2002) and RRP was performed using the anatomic technique described by Walsh (Walsh 2000). Mono or bilateral nerve-sparing procedure was performed whenever possible. In both groups, limited pelvic lymphadenectomy was performed when total serum PSA level was 10 ng/mL and/or Gleason score = 7</p> <p>Pain control: standard analgesic protocol included administration of tramadol 1 mg/kg and ketoprofen 100 mg 30 min before the end of the operation and tramadol 200 mg + ketoprofen 200 mg diluted in 500 mL of saline solution infused at 30 mL/h starting from admission to the recovery room until 08.00 on POD 1. If any further analgesia was requested by the participant (VAS > 3) during the day of the operation, 100 mg of pethidine was administered intravenously every 8 hours. If pain was present after POD 1 (VAS > 3), 100 mg ketoprofen could be administered intramuscularly a maximum of 3 times in 24 h</p>

Guazzoni 2006 (Continued)

Outcomes	Estimated intra-operative blood loss and autologous or homologous transfusions <ul style="list-style-type: none">• How measured: not reported• Time points measured: not reported• Time points reported: not reported Validated 10-point VAS for pain <ul style="list-style-type: none">• How measured: 10-point VAS score• Time points measured: 3 h postoperatively and on POD 1, 2 and 3• Time points reported: 3 h postoperatively and on POD 1, 2 and 3 Catheterisation time, hospital stay, peri-operative complications <ul style="list-style-type: none">• How measured: medical record• Time points measured: on POD 1, 2, 3, 5, and 6• Time points reported: on POD 1, 2, 3, 5, and 6	
Funding sources	Not reported	
Declarations of interest	Not reported	
Notes	Protocol: not reported Language of publication: English	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from publication: "Using a computer-generated randomisation table" Judgement comments: randomisation of participants was achieved using a computer-generated randomisation table
Allocation concealment (selection bias)	Unclear risk	Judgement comments: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comments: blinding might be impossible for at least some people in surgical trial
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Judgement comments: not described
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement comments: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Oncologic outcomes	Unclear risk	Judgement comments: review outcomes were not described and protocol was not published
Incomplete outcome data (attrition bias) Quality of life outcomes	Unclear risk	Judgement comments: review outcomes were not described and protocol was not published

Guazzoni 2006 (Continued)

Incomplete outcome data (attrition bias) Overall surgical complications, serious surgical complications, hospital stay, and blood transfusions	Low risk	Judgement comments: all participants were included in analysis
Incomplete outcome data (attrition bias) Postoperative pain	Low risk	Judgement comments: all participants were included in analysis
Selective reporting (reporting bias) Oncologic outcomes	Unclear risk	Judgement comments: review outcomes were not described and protocol was not published
Selective reporting (reporting bias) Quality of life outcomes	Unclear risk	Judgement comments: review outcomes were not described and protocol was not published
Selective reporting (reporting bias) Overall surgical complications, serious surgical complications, postoperative pain, hospital stay, and blood transfusions	Unclear risk	Judgement comments: review outcomes were well described but protocol was not published
Other bias	Unclear risk	Judgement comments: there were statistical differences in nerve sparing procedure between each group

Yaxley 2016

Methods	Study design: RCT (1:1) Setting/Country: single centre/Australia Dates when study was conducted: 23 August 2010-25 November 2014
Participants	Inclusion criteria: men newly diagnosed with clinically localised prostate cancer and had chosen surgery as their treatment approach; able to read and speak English; with no previous history of head injury, dementia, or psychiatric illness; no other concurrent cancer; an estimated life expectancy of 10 years or more; and aged 35-70 years Exclusion criteria: men with evidence of non-localised prostate cancer clinically; PSA > 20 ng/mL; previous laparoscopic hernia repair; previous pelvic radiotherapy for major pelvic surgery; and another malignancy within the past 5 years with the exception of non-melanoma skin cancer Total number of participants randomly assigned: 326 Group A (RARP) <ul style="list-style-type: none"> Number of all participants randomly assigned: 163 Age (years): 59.64 ± 6.63 Prostate volume (mL): not reported PSA (ng/mL): 7.41 ± 4.10

Yaxley 2016 (Continued)

- Pathologic stage: extraprostatic extension (35%), seminal vesicle involvement (3%), surgical margins positive (15%)
- Pathologic Gleason score: ≤ 6 (4%), 7 (86%), ≥ 8 (10%)

Group B (ORP)

- Number of all participants randomly assigned: 163
- Age (years): 60.38 ± 5.81
- Prostate volume (mL): not reported
- PSA (ng/mL): 7.57 ± 4.07
- Pathologic stage: extraprostatic extension (32%), seminal vesicle involvement (6%), surgical margins positive (10%)
- Pathologic Gleason score: ≤ 6 (3%), 7 (86%), ≥ 8 (11%)

Interventions
Group A: RARP
Group B: ORP

Surgeon: every procedure was done by the same surgeon who had the most expertise in each approach (over 1000 RARPs with more than 2000 radical procedures by trial completion)

Surgical procedure: cavernous nerve preservation was undertaken on individual surgeon discretion based on clinical staging. A pelvic lymph node dissection was done on protocol for a serum PSA greater than 10 ng/mL, a palpable nodule on digital rectal examination, or primary Gleason grade 4 or higher on biopsy sampling (i.e. Gleason 4 + 3, 4 + 4, 4 + 5, or 5 + 4). A standardised template for lymphadenectomy was used by both surgeons, with the upper margin of dissection at the ureteric crossing of the iliac vessels.

Pain control: epidural or spinal anaesthesia was not used routinely in either group.

Outcomes
Primary outcome:

- Urinary function (urinary domain of EPIC)
- Sexual function (sexual domain of EPIC and IIEF)
- Oncological outcomes (positive surgical margin status and biochemical and imaging evidence of progression at 24 months)

How measured: EPIC and IIEF questionnaire, medical record

Time points measured: at baseline, 6 weeks, 12 weeks, 6 months, 12 months, and 24 months

Time points reported: at baseline, 6 weeks, and 12 weeks

Secondary outcome:

- Pain: Surgical Pain Scale
- Physical and mental functioning: Short Form 36 Health Survey (SF-36)
- Fatigue: vitality domain of SF-36
- Preference based utility scores: Validity and Reliability of the Assessment of Quality of Life
- Bowel function: EPIC
- Cancer specific distress: Revised Impact of Events
- Psychological distress: Hospital Anxiety and Depression Scale
- Time to return to work: medical record
- International prostate symptom score: IPSS questionnaire
- Pad use: medical record
- Erection data: medical record

Time points measured: at baseline, 24 hours (pain), 1 week (pain), 6 weeks, 12 weeks, 6 months, 12 months, and 24 months

Yaxley 2016 (Continued)

Time points reported: at baseline, 24 hours (pain), 1 week (pain), 6 weeks, and 12 weeks

Funding sources	Cancer Council Queensland
Declarations of interest	No competing interests
Notes	<p>Blinded interim analysis was pre-planned and stipulated in the trial registration when 75% of the target sample size was recruited and was overseen by an independent data monitoring committee in August 2014 (n = 321)</p> <p>Protocol: Australian New Zealand Clinical Trials Registry (ACTRN: 12611000661976)</p> <p>Language of publication: English</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote from publication: "Randomisation was computer generated and occurred in blocks of ten."</p> <p>Judgement comments: randomisation was achieved via computerised database that performed block randomisation</p>
Allocation concealment (selection bias)	Unclear risk	Judgement comments: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote from publication: "After randomisation, patients were telephoned the same day to be notified of their designated surgical procedure and posted an information booklet outlining expectations for their scheduled operation."; "This was an open trial; however, study investigators involved in data analysis were blinded to each patient's condition."</p> <p>Judgement comments: participants and personnel were not blinded for assigned surgical procedure</p>
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	<p>Quote from publication: "Study investigators involved in data analysis were blinded to each patient's condition. Further a blinded central pathologist reviewed the biopsy and radical prostatectomy specimens."</p> <p>Judgement comments: study investigators were blinded against detection bias</p>
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Judgement comments: objective outcomes are not likely affected by lack of blinding
Incomplete outcome data (attrition bias) Oncologic outcomes	Low risk	Judgement comments: review outcomes were not described but protocol did not include the outcomes
Incomplete outcome data (attrition bias) Quality of life outcomes	High risk	Judgement comments: 129/163 (79.1%) in RARP and 119/163 (73.0%) in ORP were included in analysis
Incomplete outcome data (attrition bias) Overall surgical complications, serious surgical complications, hospital	Low risk	Judgement comments: 157/163 (96.3%) in RARP and 151/163 (92.6%) in ORP were included in analysis

Yaxley 2016 (Continued)

stay, and blood transfusions

Incomplete outcome data (attrition bias) Postoperative pain	High risk	Judgement comments: 130/163 (79.7%) in RARP and 120/163 (73.6%) in ORP were included in analysis
Selective reporting (reporting bias) Oncologic outcomes	Low risk	Judgement comments: review outcomes were not described but protocol did not included the outcomes
Selective reporting (reporting bias) Quality of life outcomes	Low risk	Judgement comments: review outcomes were well described and protocol was published
Selective reporting (reporting bias) Overall surgical complications, serious surgical complications, postoperative pain, hospital stay, and blood transfusions	Low risk	Judgement comments: review outcomes were well described and protocol was published
Other bias	Low risk	Judgement comments: none detected

EPIC: Expanded Prostate Cancer Index Composite; **IIEF:** International Index of Erectile Function; **LRP:** laparoscopic prostatectomy; **ORP:** open radical retropubic prostatectomy; **POD:** postoperative day; **PSA:** prostate-specific antigen; **RARP:** robotic-assisted radical prostatectomy; **RCT:** randomised controlled trial; **VAS:** visual analogue scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Magheli 2014	Non-RCT

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Laparoscopic radical prostatectomy/ robotic-assisted radical prostatectomy vs open radical prostatectomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urinary QoL (short term)	1	248	Mean Difference (IV, Random, 95% CI)	-1.30 [-4.65, 2.05]
2 Sexual QoL (short term)	1	248	Mean Difference (IV, Random, 95% CI)	3.90 [-1.84, 9.64]
3 Surgical complications (short term)	1	308	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.16, 1.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Serious postoperative complications (short term)	1	308	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.02, 1.32]
5 Postoperative pain (at 1 day)	2	423	Mean Difference (IV, Random, 95% CI)	-1.05 [-1.42, -0.68]
6 Postoperative pain (at 1 week)	2	416	Mean Difference (IV, Random, 95% CI)	-0.78 [-1.40, -0.17]
7 Postoperative pain (at 12 weeks)	1	250	Mean Difference (IV, Random, 95% CI)	0.01 [-0.32, 0.34]
8 Hospital stay (short term)	1	308	Mean Difference (IV, Random, 95% CI)	-1.72 [-2.19, -1.25]
9 Blood transfusion (short term)	2	428	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.12, 0.46]

Analysis 1.1. Comparison 1 Laparoscopic radical prostatectomy/ robotic-assisted radical prostatectomy vs open radical prostatectomy, Outcome 1 Urinary QoL (short term).

Analysis 1.2. Comparison 1 Laparoscopic radical prostatectomy/ robotic-assisted radical prostatectomy vs open radical prostatectomy, Outcome 2 Sexual QoL (short term).

Analysis 1.3. Comparison 1 Laparoscopic radical prostatectomy/ robotic-assisted radical prostatectomy vs open radical prostatectomy, Outcome 3 Surgical complications (short term).

Analysis 1.4. Comparison 1 Laparoscopic radical prostatectomy/ robotic-assisted radical prostatectomy vs open radical prostatectomy, Outcome 4 Serious postoperative complications (short term).

Analysis 1.5. Comparison 1 Laparoscopic radical prostatectomy/ robotic-assisted radical prostatectomy vs open radical prostatectomy, Outcome 5 Postoperative pain (at 1 day).

Analysis 1.6. Comparison 1 Laparoscopic radical prostatectomy/ robotic-assisted radical prostatectomy vs open radical prostatectomy, Outcome 6 Postoperative pain (at 1 week).

Analysis 1.7. Comparison 1 Laparoscopic radical prostatectomy/ robotic-assisted radical prostatectomy vs open radical prostatectomy, Outcome 7 Postoperative pain (at 12 weeks).

Analysis 1.8. Comparison 1 Laparoscopic radical prostatectomy/ robotic-assisted radical prostatectomy vs open radical prostatectomy, Outcome 8 Hospital stay (short term).

Analysis 1.9. Comparison 1 Laparoscopic radical prostatectomy/ robotic-assisted radical prostatectomy vs open radical prostatectomy, Outcome 9 Blood transfusion (short term).

ADDITIONAL TABLES

Table 1. Baseline characteristics

Study name	Trial period (year to year)	Country	Setting	Description of participants	Intervention(s) and comparator(s)	Duration of intervention (duration of follow-up)	Age (yrs)	PSA (ng/mL)	Pathologic stage
Guazzoni 2006	NR	Italy	Single surgeon	Men aged < 70 years, clinically organ-confined disease (cT1 - cT2), total serum PSA < 20 ng/dL, Gleason score ≤ 7	LRP	6 days	62.29 ± 8.2	6.9 ± 2.9	T2 (75.0%), T3 (25%), surgical margin positive (26.0%)
					ORP		62.9 ± 7.4	6.5 ± 3.0	T2 (73.3%), T3 (26.6%), surgical margin positive (21.6%)
Yaxley 2016	2010 to 2014	Australia	Single centre	Men aged 35-70 years with newly diagnosed with clinically localised prostate cancer	RARP	12 weeks	59.64 ± 6.63	7.41 ± 4.10	Extraprostatic extension (35%), seminal vesicle involvement (3%), surgical margins positive (15%)
					ORP		60.38 ± 5.81	7.57 ± 4.07	Extraprostatic extension (32%), seminal vesicle involvement (6%), surgical margins positive (10%)

LRP: laparoscopic prostatectomy; **NR:** not reported; **ORP:** open radical prostatectomy; **PSA:** prostate-specific antigen; **RARP:** robotic-assisted radical prostatectomy

Table 2. Participants' disposition

Study name	Intervention(s) and comparator(s)	Sample size (N)	Screened/eligible (N)	Ran-domised (N)	Analysed (N)	Finishing trial (N (%))
Guazzoni 2006	LRP	NR	NR	60	60	60 (100.0)
	ORP	NR		60	60	60 (100.0)
	Total			120	120	120 (100.0)
Yaxley 2016	RARP	200	NR/334	163	QoL: 129 Surgical outcomes: 157 ^a Pain: 130	157 (96.3)
	ORP	200		163	QoL: 119 Surgical outcomes: 151 ^a Pain: 120	151 (92.6)
	Total			326	QoL: 248 Surgical outcomes: 308 Pain: 250	308 (94.4)
Grand to-tal	All interventions			223		217
	All comparators			223		211
	Overall			446		428

^aSurgical outcomes: surgical complications, hospital stay, and blood transfusions

LRP: laparoscopic prostatectomy; **NR:** not reported; **ORP:** open radical prostatectomy; **QoL:** quality of life; **RARP:** robotic-assisted radical prostatectomy

APPENDICES

Appendix 1. CENTRAL search strategy

We performed the following search strategy in CENTRAL; 2017, issue 6 in the Cochrane Library.

1. Prostatic Neoplasms/ or Prostate Neoplasms.mp. or Prostate Neoplasm.mp. or prostate cancer.mp. or Prostate Cancers.mp. or Prostatic Cancer.mp. or Prostatic Cancers.mp. or prostatic neoplasm.mp. or prostatic neoplasms.mp.
2. Prostatectomy/ or prostatectomy.mp. or prostatectomies.mp.
3. radical.mp.
4. open.mp.
5. 2 and 3 and 4
6. (RPP or radical retropubic prostatectomy or radical retropubic prostatectomies).mp.
7. 5 or 6
8. Laparoscopy/ or laparoscopy.mp. or laparoscopies.mp. or laparoscopic.mp.

9. 2 and 8
- 10.RALP.mp.
- 11.(robot\$ assisted radical prostatectomy or robot\$ assisted radical prostatectomies).mp.
- 12.RARP.mp.
- 13.(minimally invasive radical prostatectomy or minimally invasive radical prostatectomies).mp.
- 14.MIRP.mp.
- 15.9 or 10 or 11 or 12 or 13 or 14
- 16.1 and 7 and 15
- 17.randomized controlled trial.pt.
- 18.controlled clinical trial.pt.
- 19.randomized.ab.
- 20.randomly.ab.
- 21.trial.ab.
- 22.17 or 18 or 19 or 20 or 21
- 23.exp animals/ not humans.sh.
- 24.22 not 23
- 25.16 and 24

Appendix 2. MEDLINE search strategy

The MEDLINE search was performed on the Ovid platform (1946-present with daily update (9th June 2017))

1. Prostatic Neoplasms/ or Prostate Neoplasms.mp. or Prostate Neoplasm.mp. or prostate cancer.mp. or Prostate Cancers.mp. or Prostatic Cancer.mp. or Prostatic Cancers.mp. or prostatic neoplasm.mp. or prostatic neoplasms.mp.
2. Prostatectomy/ or prostatectomy.mp. or prostatectomies.mp.
3. radical.mp.
4. open.mp.
5. 2 and 3 and 4
6. (RPP or radical retropubic prostatectomy or radical retropubic prostatectomies).mp.
7. 5 or 6
8. Laparoscopy/ or laparoscopy.mp. or laparoscopies.mp. or laparoscopic.mp.
9. 2 and 8
- 10.RALP.mp.
- 11.(robot\$ assisted radical prostatectomy or robot\$ assisted radical prostatectomies).mp.
- 12.RARP.mp.
- 13.(minimally invasive radical prostatectomy or minimally invasive radical prostatectomies).mp.
- 14.MIRP.mp.
- 15.9 or 10 or 11 or 12 or 13 or 14
- 16.1 and 7 and 15
- 17.randomized controlled trial.pt.
- 18.controlled clinical trial.pt.
- 19.randomized.ab.
- 20.randomly.ab.
- 21.trial.ab.
- 22.17 or 18 or 19 or 20 or 21
- 23.exp animals/ not humans.sh.
- 24.22 not 23
- 25.16 and 24

Appendix 3. EMBASE search strategy

The EMBASE search was performed on the Ovid platform (1974-June 2017)

1. Prostatic Neoplasms/ or Prostate Neoplasms.mp. or Prostate Neoplasm.mp. or prostate cancer.mp. or Prostate Cancers.mp. or Prostatic Cancer.mp. or Prostatic Cancers.mp. or prostatic neoplasm.mp. or prostatic neoplasms.mp.
2. Prostatectomy/ or prostatectomy.mp. or prostatectomies.mp.

3. radical.mp.
4. open.mp.
5. 2 and 3 and 4
6. (RPP or radical retropubic prostatectomy or radical retropubic prostatectomies).mp.
7. 5 or 6
8. Laparoscopy/ or laparoscopy.mp. or laparoscopies.mp. or laparoscopic.mp.
9. 2 and 8
- 10.RALP.mp.
- 11.(robot\$ assisted radical prostatectomy or robot\$ assisted radical prostatectomies).mp.
- 12.RARP.mp.
- 13.(minimally invasive radical prostatectomy or minimally invasive radical prostatectomies).mp.
- 14.MIRP.mp.
- 15.9 or 10 or 11 or 12 or 13 or 14
- 16.1 and 7 and 15
- 17.randomized controlled trial.pt.
- 18.controlled clinical trial.pt.
- 19.randomized.ab.
- 20.randomly.ab.
- 21.trial.ab.
- 22.17 or 18 or 19 or 20 or 21
- 23.exp animals/ not humans.sh.
- 24.22 not 23
- 25.16 and 24

CONTRIBUTIONS OF AUTHORS

Dragan Ilic initiated the review and wrote the initial protocol. He conducted the literature search, reviewed abstracts and full-text studies for inclusion, performed quality assessment, data extraction, analysis, and wrote the review. Guarantor of the review.

Sue Evans wrote the initial protocol. She conducted the literature search, reviewed abstracts and full-text studies for inclusion, performed analysis, and wrote the review.

Christie Allan reviewed abstracts and full-text studies for inclusion, performed quality assessment, and contributed to the writing of the review.

Jae Hung Jung performed quality assessment, data extraction, analysis and contributed to the writing of the review.

Declan Murphy wrote the initial protocol. He contributed to the data analysis and writing of the review.

Mark Frydenberg wrote the initial protocol. He contributed to the data analysis and writing of the review.

DECLARATIONS OF INTEREST

Dragan Ilic: none declared

Sue Evans: none declared

Christie Allan: none declared

Jae Hung Jung: none declared

Declan Murphy: none declared

Mark Frydenberg: none declared

SOURCES OF SUPPORT

Internal sources

- Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Australia.
- Centre of Research Excellence in Patient Safety, School of Public Health and Preventive Medicine, Monash University, Australia.

- Department of Urology, Yonsei University Wonju College of Medicine, Korea, South.
- Cancer Surgery, Peter MacCallum Cancer Centre, Australia.
- Department of Surgery, Monash University, Australia.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- In the original protocol (Ilic 2012) we had stated that non-RCTs would be eligible for inclusion in the review to examine secondary objectives. It was also stated that only articles in English would be considered eligible for inclusion. Disease-specific and general quality of life was originally listed as a secondary outcome but have been moved up to be primary outcomes. The search strategy for non-RCTs has been removed from the review. The title has been amended from the original title in the protocol. All these changes were made after discussion and with the formal agreement of Cochrane Urology.
- We have described experimental interventions and control in greater detail than before.
- We further specified the methods of measurement of primary and secondary outcomes in addition to the description of main outcomes for 'Summary of findings' tab

INDEX TERMS**Medical Subject Headings (MeSH)**

Laparoscopy [adverse effects] [*methods]; Organ Size; Prostate [pathology]; Prostate-Specific Antigen [blood]; Prostatectomy [adverse effects] [*methods]; Prostatic Neoplasms [blood] [mortality] [pathology] [*surgery]; Quality of Life; Randomized Controlled Trials as Topic; Robotic Surgical Procedures [adverse effects] [*methods]; Sexual Behavior; Urination

MeSH check words

Humans; Male; Middle Aged