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Laparoscopic and robot-assisted vs open radical prostatectomy for the treatment of localized prostate cancer: a Cochrane systematic review

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ABSTRACT

To determine the effects of laparoscopic radical prostatectomy (LRP), or robotic-assisted radical prostatectomy (RARP), compared to open radical prostatectomy (ORP) in men with localised prostate cancer.

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 included all randomised or pseudo-randomised controlled trials with a direct comparison of LRP and RARP to ORP. Two review authors independently examined full-text reports, identified relevant studies, assessed the eligibility of studies for inclusion, extracted data and assessed risk of bias. We performed statistical analyses using a random-effects model and assessed the quality of the evidence (QoE) according to GRADE. 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 included two unique studies with 446 randomised participants with clinically localised prostate cancer. All available outcome data were short-term (up to 3 months). We found no study that addressed the outcome of prostate cancer-specific survival. Based on one trial, RARP likely results in little to no difference in urinary quality of life (mean difference [MD] -1.30, 95% confidence interval [CI] -4.65 to 2.05; moderate QoE) and sexual quality of life (MD 3.90, 95% CI -1.84 to 9.64; moderate QoE). No study addressed the outcomes of biochemical recurrence-free survival or overall survival.

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Based on one trial, RARP may result in little to no difference in overall surgical complications (risk ratio [RR] 0.41, 95% CI 0.16 to 1.04; low QoE) or serious postoperative complications (RR 0.16, 95% CI 0.02 to 1.32; low QoE). 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; low QoE) and up to one week (MD -0.78, 95% CI -1.40 to -0.17; low QoE). 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; moderate QoE). Based on one study, RARP likely reduces the length of hospital stay (MD -1.72, 95% CI -2.19 to -1.25; moderate QoE). Based on two studies, LRP or RARP may reduce the frequency of blood transfusions (RR 0.24, 95% CI 0.12 to 0.46; low QoE). 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).

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

Keywords: prostate cancer, randomized controlled trials, surgical procedures, operative

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INTRODUCTION

Prostate cancer is a leading disease affecting men worldwide and accounting for 15% of cancers diagnosed in men. In 2012 prostate cancer accounted for 14% of the total new cancers diagnosed worldwide, and 6% of total cancer deaths in men [1, 2]. Men diagnosed with localised prostate cancer have a variety of management options available, including radical prostatectomy (RP). 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 [3-5].

RP is recommended as a front-line treatment for men diagnosed with localised prostate cancer and with a life expectancy greater than 10 years [3-5]. The late 1990s saw the introduction of laparoscopic approach (LRP) with the aim of reducing postoperative morbidity and allowing faster recovery when compared to traditional open radical prostatectomy (ORP) [6]. Initially, surgeons adopting the LRP approach needed to overcome significant technical challenges and a significant learning curve [7]. The robotic-assisted radical prostatectomy approach (RARP) was introduced in 2000s and has since been widely adopted with technical innovations (3-D visualisation, articulated instruments, tremor filtration) which addressed some of the technical limitations of LRP [8, 9].

While large prospective randomised controlled trials (RCTs) have reported the possible benefit of RP in men with low- and intermediate-risk prostate cancer, the effectiveness of LRP and RARP compared to ORP for functional or oncological outcomes remains unclear [10-13]. Therefore, we aimed to assess the effects of LRP or RARP compared to ORP in men with localised prostate cancer.

This is an abridged version of a Cochrane review published in the Cochrane Library titled 'Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer' [14].

MATERIALS AND METHODS

Search strategy and selection criteria

This systematic review and meta-analyses were based on published protocol [15]. We performed a comprehensive search using multiple database of the Cochrane Central Register of Controlled Trials (1987 to 2017, issue 6) in the Cochrane Library, MEDLINE Ovid (1946 to 9 June 2017) and EMBASE Ovid (1974 to June 2017). 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 from 2015 to 2017 for unpublished studies from annual meetings of the American Urological Association and the European Association of Urology. Searches were initially performed on

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13 December 2016 followed by an updated search on 9 June 2017. Two review authors (DI and CA) independently screened all potentially relevant records and classified studies in accordance with the criteria for each provided in the Cochrane Handbook for Systematic Reviews of Interventions [16].
We reviewed RCTs, including pseudo-RCTs.

Types of participants

We included studies recruiting men, 18 years of age or older, of any ethnicity, diagnosed with clinically localised prostate cancer. 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 intervention

The experimental intervention was LRP or RARP. The control intervention was ORP.

Types of outcomes measured

The primary outcomes of the review were prostate cancer-specific survival, urinary quality of life and sexual quality of life (assessed with a validated questionnaire such as urinary domain of Expanded Prostate Cancer Index Composite) [17]. Secondary outcomes were biochemical recurrence-free survival (defined as a prostate specific antigen value 0.2 ng/mL after RP and confirmed by at least two consecutive measurements), overall survival, overall surgical complications, serious postoperative complications (such as postoperative haemorrhage requiring admission or intervention, or life-threatening complications), postoperative pain (assessed with validated questionnaires such as visual analogue scale score), hospital stay (measured as days from admission to discharge) and blood transfusions (measured as frequencies after surgery) [4]. We have presented a 'Summary of findings' table reporting the prostate cancer-specific survival, urinary quality of life, sexual quality of life, biochemical recurrence-free survival, overall survival and overall postoperative complications according to priority.

Data collection and data extraction

Two review authors (DI and CA) independently assessed all studies using a data extraction form and followed the domain-based risk of bias evaluation as described in the Cochrane Handbook for Systematic Reviews of Interventions [16].
We planned to extract hazard ratios (HRs) with 95% confidence intervals (CIs) for time to event outcomes. We attempted to obtain numbers of events and totals for population for dichotomous outcomes and means with standard deviations or data necessary to calculate this information for continuous outcomes. We summarised data using a random-effects model. We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects.
We planned to assess heterogeneity statistically with the I^2 statistic. I^2 values of 25%, 50% and 75% were considered low, moderate and high, respectively, and values exceeding 50% were considered substantial heterogeneity [18]. Tests for funnel plot asymmetry are generally only performed when at

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least 10 studies are included in the meta-analysis. As our analysis only included two studies, tests for asymmetry would have been ineffective as they would have been unable to differentiate chance from asymmetry. We used Review Manager 5 software (The Cochrane Collaboration, Copenhagen, Denmark) to perform statistical analyses.

We planned to conduct the following subgroup analyses: LRP versus RARP; pathological tumour stage (i.e. T2 versus T3 disease). We planned to perform sensitivity in order to explore the influence of the following factor: restricting the analysis by taking into account risk of bias by excluding studies at 'high risk' or 'unclear risk'.

Summary of findings table

We presented the overall quality of the evidence for each outcome according to GRADE, which takes into account five criteria not only related to internal validity (study limitations, inconsistency, imprecision, publication bias) but also to external validity such as directness of results [19].

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RESULTS

Search results

A search of all electronic databases returned 85 citations 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 [20]. We assessed two studies as eligible for inclusion in this review [21, 22]. The flow of literature through the assessment process is shown in the flowchart (Figure 1).

Included studies

This review includes 446 randomised participants in total, of whom a total of 428 subsequently finished for the intervention and control groups. Table 1 shows the baseline characteristics of the included studies. Guazzoni et al. [21] compared LRP to ORP. LRP was performed via the trans-peritoneal route according to the Montsouris technique and ORP was performed using the anatomic technique described by Walsh [23, 24]. Single surgeons performed all procedures. Yaxley et al. [22] compared RARP to ORP. Each surgical procedure was done by the same surgeon. Pelvic lymph node dissection was performed in participants with a serum prostate specific antigen greater than 10 ng/mL, or Gleason score more than 7 in both studies. All studies 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 one included study, but epidural or spinal anaesthesia was not used routinely in the other. Study outcomes were reported at up to 12 weeks postoperatively. While Guazzoni et al. [21] did not report either funding sources or conflicts of interests, Yaxley et al. [22] was supported by Cancer Council Queensland without any competing interests.

Effect of the intervention

1. Primary Outcomes

1) Prostate cancer-specific survival

Neither of the two trials reported this outcome.

2) Urinary quality of life

Yaxley et al. [22] 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 (mean difference [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.

3) Sexual quality of life

Yaxley et al. [22] 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 limitations.

2. Secondary Outcomes

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1) Biochemical recurrence-free survival and overall survival

Neither of the two trials included in this review reported these outcomes.

2) Overall surgical complications

Yaxley et al. [22] reported data for this outcome for 308 participants (RARP 157, ORP 151). RARP likely results in little to no difference in postoperative surgical complications (risk ratio [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.

3) Serious postoperative complications

Yaxley et al. [22] 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.

4) 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 [21, 22]. 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 [22]. 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.

5) Hospital stay

Yaxley et al. [22] 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.

6) Blood transfusions

Both the included studies 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% [25], 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 one study banked two units of autologous blood, which may have increased transfusion requirements [21].

3. Subgroup analysis

We were not able to perform a subgroup analysis due to no relevant data.

4. Sensitivity analysis

We were not able to perform a sensitivity analysis due to a paucity of included studies.

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Risk of bias

Figure 2 shows summary of risk of bias assessment.

1. Allocation (selection bias)

1) Random sequence generation

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

2) Allocation concealment

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

2. Blinding of participants and personnel (performance bias)

We judged both included studies as high risk of bias.

3. Blinding of outcome assessor (detection bias)

1) 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, postoperative pain)

We rated one study as low risk of bias [22], but the other as unclear risk of bias [21].

2) Not susceptible/objective outcomes (overall survival, hospital stay, blood transfusions)

We judged both included studies as low risk of bias.

4. Incomplete outcome data (attrition bias)

1) Oncological outcomes (prostate cancer specific survival, biochemical recurrence-free survival, overall survival)

We rated one study as low risk of bias [22], but the other as unclear risk of bias [21].

2) Quality-of-life outcomes (urinary quality of life, sexual quality of life)

We rated one study as high risk of bias [22], but the other as unclear risk of bias [21].

3) Overall surgical complications, serious postoperative complications, hospital stay, and blood transfusions

We judged both included studies as low risk of bias.

4) Postoperative pain

We rated one study as low risk of bias [21], but the other as high risk of bias [22].

5. Selective reporting (reporting bias)

We rated one study, which had a published protocol, as low risk of bias [22], but the other as unclear risk of bias [21].

6. Other potential sources of bias

We rated one study as low risk of bias [22], but the other as unclear risk of bias due to an imbalance

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in the number of nerve-sparing procedures between the interventions, which may have affected the prognosis [21].

Summary of findings table

We summarised the results in a summary of findings table in accordance with GRADE methodology (Table 2).

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DISCUSSION

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 [7, 26-30]. 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 [27, 28, 30, 31]. Conversely, urinary and sexual quality of life have been reported in observational studies to be significantly better in men receiving RARP compared to ORP [29]. However, evidence from previous systematic reviews of non-RCTs has uniformly concluded that the

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quality of the evidence base on observational studies is low [16, 32]. 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 [27, 29, 31].

This review has some limitations with regards to applicability of evidence. It is based on only two RCTs with relatively small sample sizes and event rates conducted at tertiary care centres with expert surgeons [21, 22]. This narrow evidence base stands in marked contrast to the widespread use of RARP in many countries, in particular in the USA [33]. 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 [34, 35]. 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 to, among other things, magnification of the operative field and 3-D imaging, device acquisition and maintenance/service are costly [8, 9, 26]. However, an assessment of the cost-effectiveness of LRP/RARP was outside the scope of this review. Given that the indication for radical surgery is motivated by men's concern about prostate cancer-related morbidity and mortality, 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 [32].

Whilst there is an urgent need to raise methodological standards for clinical research on new urologic procedures and devices, the reality of creating future RCTs may be restricted by the challenges of conducting controlled trials of surgical interventions [36]. A better understanding of the impact of LRP/RARP on oncological outcomes is needed.

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CONFLICT OF INTEREST

The authors have no external funding sources or conflicts of interest to disclose.

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Table 1. Baseline characteristics of the included studies

Study name	Trial period (year to year)	Setting/country	Total No. of randomized participants	Description of participants	Intervention (n) and comparator (n)	Age (mean, years)	PSA (mean, ng/mL)	Pathologic stage (n)	Duration of intervention (duration of follow-up)
Guazzoni 2006 [20]	Not reported	Single surgeon /Italy	120	Men aged < 70 years, clinically organ-confined disease (cT1 - cT2), total serum PSA < 20 ng/mL, Gleason score ≤ 7	LRP (60) and ORP (60)	62	6.7	pT2: 89 (74.1%) pT3: 31 (26.9%) Positive surgical margin: 29 (24.1%)	6 days
Yaxley 2016 [21]	2010 to 2014	Single centre /Australia	326	Men aged 35-70 years with newly diagnosed with clinically localised prostate cancer	RARP (163) and ORP (163)	60	7.4	Extraprostatic extension: 104 (33.7%) Seminal vesicle involvement: 14 (4.5%) Positive surgical margins: 38	12 weeks

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(12.3%)

LRP, laparoscopic prostatectomy; ORP, open radical prostatectomy; PSA, prostate-specific antigen; RARP, robotic-assisted radical prostatectomy.

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Table 2. Summary of findings

LRP/RARP compared to ORP for the treatment of localised prostate cancer					
Participants: men with localised prostate cancer Setting: single surgeon or single centre Intervention: LRP/RARP Control: ORP					
Outcomes	**№ of participants (studies)**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with ORP	**Risk difference with LRP/RARP**
Prostate cancer specific survival - not reported	-	-	-	-	-

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Urinary incontinence assessed with: Expanded Prostate Cancer Index Composite[a] follow up: mean 3 months	248 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	-	The mean urinary incontinence (short term) was **83.8**	MD **1.3 lower** (4.65 lower to 2.05 higher)
Erectile dysfunction assessed with: Expanded Prostate Cancer Index Composite[a] follow up: mean 3 months	248 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	-	The mean erectile dysfunction (short term) 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 follow up: range 1 weeks to 3 months	308 (1 RCT)	⊕⊕◯◯ LOW [b,c]	**RR 0.41** (0.16 to 1.04)	**Study population**	
				40 per 1,000	**23 fewer per 1,000** (33 fewer to 2 more)
				Moderate [d]	

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	238 per 1,000	**140 fewer per 1,000** (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).

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 limitations: 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 et al. [25].

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

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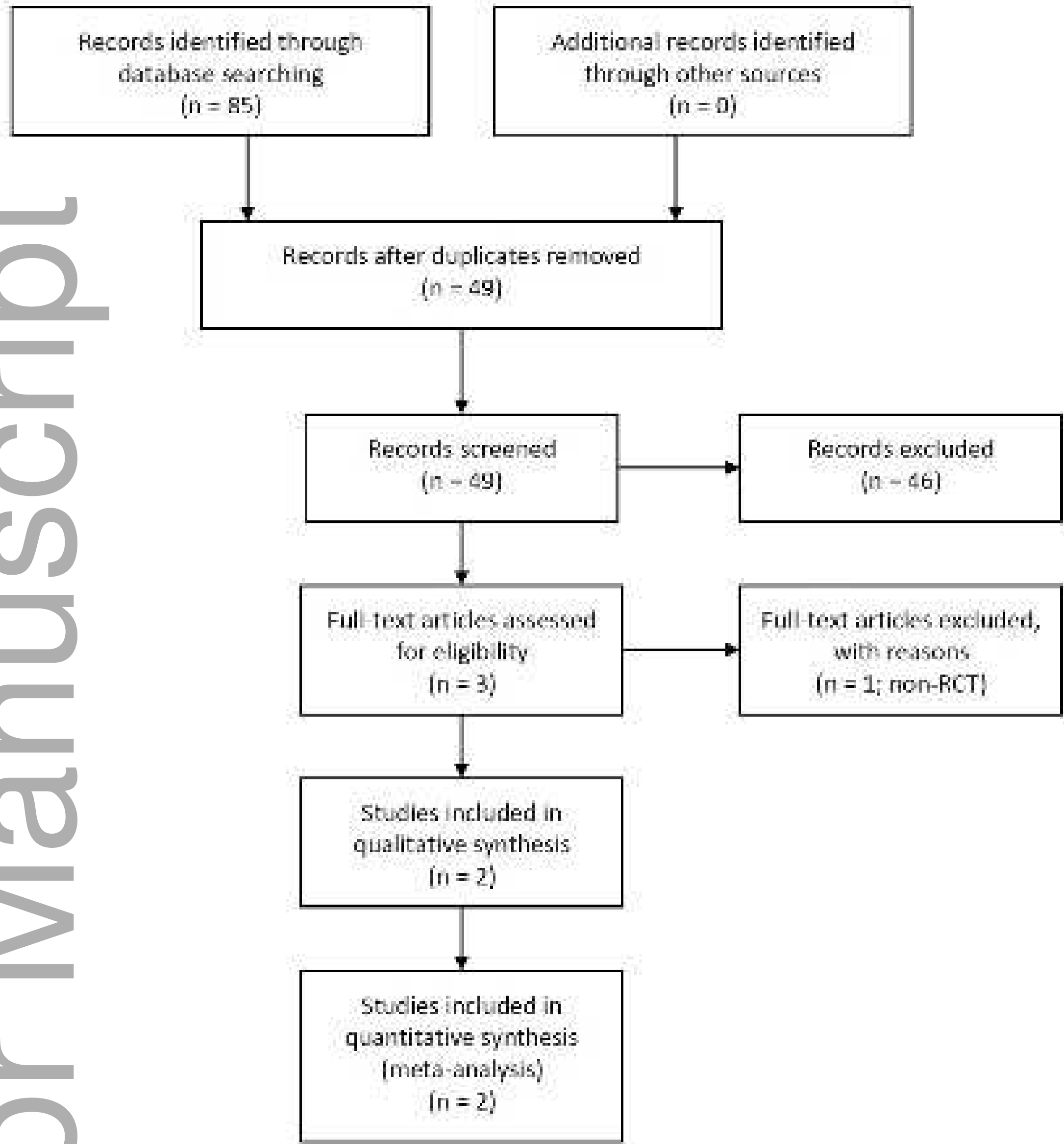

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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias): Subjective outcomes	Blinding of outcome assessment (detection bias): Objective outcomes	Incomplete outcome data (attrition bias): Oncologic outcomes	Incomplete outcome data (attrition bias): Quality of life outcomes	Incomplete outcome data (attrition bias): Postoperative pain	Incomplete outcome data (attrition bias): Other outcomes	Selective reporting (reporting bias)	Other bias
Guazzoni 2006	+	?	-	?	+	?	?	+	+	?	?
Yaxley 2016	+	?	-	+	+	+	-	-	+	+	+

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