Laparoscopic versus Robotic-Assisted Radical Prostatectomy for the Treatment of Localised Prostate Cancer: A Systematic Review

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Key Words
Prostate cancer · Systematic review · Prostatectomy · Laparoscopic · Robotic

Abstract
Background: Prostate cancer is a prominent form of cancer diagnosed in men living in developed countries, for which radical prostatectomy is a common frontline treatment. The aim of this systematic review was to determine whether robot-assisted laparoscopic radical prostatectomy (RALP) is more effective in the treatment of localised prostate cancer, compared to laparoscopic radical prostatectomy (LRP).

Methods: An electronic search of Medline, Scopus, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials (Central) was performed up until December 2014. Randomised controlled trials (RCTs) that offered a direct comparison of laparoscopic and robotic techniques were eligible for inclusion in this review.

Results: A total of 93 articles were identified through the literature search, of which 2 were included in this review. Meta-analysis of 2 studies identified a significantly higher rate of return of erectile function in the RALP group (relative risk (RR) 1.51; 95% confidence interval (CI) 1.19, 1.92). A similar effect was observed with return to continence function (RR 1.14; 95% CI 1.04, 1.24).

Conclusions: This systematic review offers the first evaluation of evidence from RCTs with respect to the effectiveness of RALP and LRP in the treatment of localised prostate cancer. Preliminary results suggest that RALP was more efficient at preserving the erectile function and continence in comparison to LRP.

Introduction
Prostate cancer is a disease most frequently occurring in men worldwide, second to lung cancer with a global, age-standardised incidence rate of 31.1% [1, 2]. In 2012, an estimated 1.1 million men were diagnosed with the disease – accounting for 15% of all cancers diagnosed in men, at that time [3]. The highest burden of this disease can be seen in developed regions, where 70% of all prostate cancer diagnoses occur [3]. Prostate cancer incidence varies more than 25-fold worldwide, with highest rates seen in Australia/New Zealand, Northern America and Europe [3].

For men diagnosed with localised prostate cancer, a variety of treatment options exist. Radical prostatectomy is a common frontline treatment; it is via an open, laparoscopic or robotic-assisted laparoscopic approach [4, 5]. Other interventions include active surveillance (or watchful waiting), radiation therapy, hormone therapy or a combination of these therapies [4, 5]. Surgical approaches continue to evolve and patient demand for prostatec-
tomy continues to increase. Technical modifications have expanded beyond open surgical approaches to include laparoscopic radical prostatectomy (LRP) and robot-assisted laparoscopic prostatectomy (RALP) [6]. These new-generation techniques aim at reducing the risk of prostate cancer-specific mortality, while minimising treatment-related morbidity and maintaining patient quality of life [6].

Robot-assisted systems have been introduced in an attempt to reduce the difficulty involved in performing complex laparoscopic procedures. It has been suggested that RALP facilitates a simplified version of the learning process, allowing quicker reduction in operative time than what pure LRP can do. However, several systematic reviews of observational studies have reported no significant difference between the 2 techniques [6, 7] – with, operative time, urinary continence, erectile function, blood loss and positive margin rate all reported as statistically insignificant. Methodological limitations associated with observational studies have heeded the call for prospective, comparative studies [6].

Men diagnosed with localised prostate cancer face an important decision to make with respect to treatment. This decision-making process is commonly informed and shared with their clinician [8]. Estimated survival, blood loss during surgery, hospital length of stay, surgical margin status, urinary continence, erectile function, and other quality of life indicators are clinically important outcomes that patients and clinicians must consider when considering treatment options [9]. The body of literature examining the effectiveness of RALP is currently limited to observational studies of (mostly) low methodological quality [6, 7].

Randomised controlled trials (RCTs) comparing the effectiveness of RALP and LRP are limited; yet a comprehensive summary of this level 1 evidence is required to provide clinicians and patients alike with a complete picture of the current evidence. The primary objective of this systematic review was to determine whether RALP is more effective than LRP in the treatment of localised prostate cancer with respect to all-cause and prostate cancer-specific mortality. Secondary objectives of the review included assessing the impact of the interventions with respect to adverse events and patient quality of life.

Materials and Methods

All RCTs that included men diagnosed with localized prostate cancer were eligible for inclusion in this systematic review. Studies were eligible for inclusion if the intervention included RALP and the comparison LRP (or vice versa). The primary outcome of this review was mortality (both prostate specific and all-cause). Secondary outcomes included biochemical recurrence-free survival, operation time, blood loss, length of stay, positive surgical margin (PSM), continence, erectile function and quality of life.

An electronic search of Medline, Scopus, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials (Central) was carried out up until December 2014. No language or other limitations were imposed. The search strategy used for Medline and adopted for other databases included the following points: (1) prostatic neoplasms/; (2) prostate cancer.mp; (3) prostatectomy/; (4) prostatectomy.mp; (5) radical prostatectomy.mp; (6) laparoscopic prostatectomy.mp; (7) laparoscopy/; (8) laparoscopy.mp; (9) open LAP.mp; (10) robot$ assisted laparoscopic prostatectomy.mp; (11) RALP.mp; (12) robot$ assisted radical prostatectomy.mp; (13) RARP.mp; (14) minimally invasive radical prostatectomy.mp; (15) MIRP.mp; (16) 1 or 2; (17) 3 or 4 or 5; (18) 6 or 7 or 8 or 9; (19) 17 and 18; (20) 10 or 11 or 12 or 13 or 14 or 15; (21) 17 and 20; (22) 16, 19 and 21; (23) limit to randomised trials.

Two reviewers (C.A. and D.I.) independently screened the titles and abstracts of all articles returned from the electronic search of the literature. Articles deemed to meet the selection criteria were sources for full-text and they were reviewed before a decision to include/exclude was made. Any discrepancies were resolved by holding discussions between the reviewers.

Two reviewers (C.A. and D.I.) independently extracted the data from included studies. Data extracted included participant demographics, study methodology and results. Any disagreements were resolved through discussions. A risk of bias assessment was conducted on all included trials using the Cochrane Collaboration’s risk of bias tool [10]. Two authors independently appraised the sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, outcome data, and selective-outcome reporting for each included study. Each criterion was graded as ‘met’, ‘unmet’, ‘unclear’ or ‘not appropriate’. Any discrepancies were resolved through discussions between the reviewers.

Statistical analysis was performed according to the statistical guidelines referenced in the Cochrane Handbook for Systematic Reviews of Interventions [10]. Dichotomous outcomes were expressed as relative risk (RR) with 95% confidence intervals (CIs), while continuous outcomes were expressed as mean difference. A random-effects model was used for meta-analysis, yielding a more conservative effect if heterogeneity is present [10]. Statistical heterogeneity was analyzed with the I^2 statistic. An I^2 value above 75% was considered to be an indicator of considerable heterogeneity [10].

Results

A total of 93 articles were identified through the literature search, of which 88 were excluded from review (fig. 1). Studies were excluded if they were not RCTs, did not include RALP and LRP, or had a population or outcome that did not meet inclusion criteria. Full text examination identified three duplicate publications. Subse-
quently, a total of 2 studies were included in the final systematic review. Information on study methodology, participants, intervention and outcomes for included studies is detailed in table 1. Risk of bias for both of the included studies is illustrated in figure 2 and was determined as follows: (1) Asimakopoulos et al. [11]: ‘unclear risk’ of bias; (2) Porpiglia et al. [12]: ‘unclear risk’ of bias.

Neither study provided published data relevant to the primary outcome of this review (i.e. mortality). The mean operative time and estimated blood loss were reported as similar by Aimakopoulos et al. [11], with no significant difference in blood transfusion rates between LRP and RALP. No difference in the mean hospital stay between the groups was reported in the study by Porpiglia et al. [12]. Both studies reported data on biochemical recurrence-free survival, PSM rate, erectile function and continence, permitting a meta-analysis of this data.

Rates of biochemical recurrence-free survival were not significantly different between the RALP and LRP groups (RR 1.01; 95% CI 0.91, 1.12). No significant difference was identified between the groups with respect to the rates of PSM (RR 1.39; 95% CI 0.81, 2.41). Return of erectile function (potency) was significantly higher in patients receiving the RALP treatment in comparison to the LRP group (RR 1.51; 95% CI 1.19, 1.92; fig. 3). Similarly, a significantly increased rate of return to continence was demonstrated in RALP patients (RR 1.14; 95% CI 1.04, 1.24; fig. 4).

**Discussion**

Two RCTs with a total of 232 participants were included in this systematic review. Neither of the studies reported on prostate cancer-specific or all-cause mortality; however, some adverse events were noted. Both studies differed in terms of methodological design, including recruitment, intervention allocation, implementation and outcome assessment. Despite lack of data on mortality, both of the studies collected data on biochemical recurrence-free survival and found no difference between the 2 techniques. However, data from both studies indicated better return to continence and erectile function for patients receiving the RALP intervention.

The best evidence available to examine the effectiveness of RALP vs. LRP is offered by randomized controlled trials. However, performing such a trial to answer this clinical question is difficult, as patients may be unwilling to accept the idea of randomisation to a surgical technique, given the life-impacting outcomes. Subsequently, evidence from retrospective and non-randomised comparative studies has informed practice to date.

Although limited by numbers, results from the 2 RCTs in this systematic review mirror findings reported in observational studies [6, 13]. The rate of blood loss and transfusion rates between LRP and RALP patients has been reported to differ across observational data – with the review by Ficarra et al. [6] reporting outcomes, while the review by Coelho et al. [13] reported decreased operative blood loss in RALP patients. Variations in length of hospital stay have been reported in observational studies [6]. In our systematic review, only the study by Porpiglia et al. [12] reported length of stay, concluding no significant difference between the groups. No significant complications were noted in either of the RCTs included in this trial – mirroring data from observational studies [6, 7].

What is evident from observational studies is that surgeon experience and surgical volume are clear factors influencing good patient outcomes [7]. It has been suggested that the learning curve for techniques such as RALP is between 200 and 250; before rates of continence and PSM
plateau to a level that is equivalent to radical prostatectomy [14, 15]. This learning curve is typical of first-generation urologists whose focus was the acquisition of the surgical technique, rather than the current second-generation urologists who have been able to focus on refining the technique, thereby reducing the length of the learning curve [16]. Although a surgeon’s vast and intense experience is associated with beneficial patient outcomes [17], it should be noted that surgical volume is also an important predictor of patient outcomes. Perioperative mortality, complications, length of stay, PSM and recurrence rates are reduced in high-volume centres and with high-volume surgeons [18].

A major confounding factor of this review is that the intervention is multifactorial – not only is the surgical intervention assessed, but individual surgeon skill influences the effectiveness of its implementation. Both of the RCTs included in this review had surgeons using different techniques and with different levels of experience in administering the RALP and LRP interventions. Asimakopoulos et al. [11] reports that over 900 LRPs and 300 RALPs were performed, while Porpiglia et al. [12] reports that >600 LRPs and 100 RALPs were performed. Although the extent of a surgeon’s experience is disclosed, it is not apparent what effect surgical volume has in the included trials. Having only 2 RCTs eligible for inclusion...
Fig. 2. Risk of bias summary.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Robotic Events</th>
<th>Laparoscopic Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk ratio M-H, Random, 95% Cl</th>
<th>Risk ratio M-H, Random, 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asimakopoulos 2011</td>
<td>22</td>
<td>52</td>
<td>44</td>
<td>0.00</td>
<td>1.81 [0.99, 3.17]</td>
<td></td>
</tr>
<tr>
<td>Porpiglia 2013</td>
<td>48</td>
<td>60</td>
<td>68</td>
<td>0.00</td>
<td>1.45 [1.12, 1.89]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>112</td>
<td>120</td>
<td>232</td>
<td>0.00</td>
<td>1.51 [1.19, 1.92]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (p = 0.46); I² = 0% Test for overall effect: Z = 3.43 (p = 0.0006)</td>
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Fig. 3. Meta-analysis of RALP vs. LRP – outcome: erectile function.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Robotic Events</th>
<th>Laparoscopic Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk ratio M-H, Random, 95% Cl</th>
<th>Risk ratio M-H, Random, 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asimakopoulos 2011</td>
<td>49</td>
<td>52</td>
<td>50</td>
<td>0.00</td>
<td>1.13 [0.99, 1.29]</td>
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<tr>
<td>Porpiglia 2013</td>
<td>57</td>
<td>60</td>
<td>60</td>
<td>0.00</td>
<td>1.14 [1.00, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>112</td>
<td>120</td>
<td>232</td>
<td>0.00</td>
<td>1.14 [1.04, 1.24]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (p = 0.93); I² = 0% Test for overall effect: Z = 2.72 (p = 0.0006)</td>
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Fig. 4. Meta-analysis of RALP vs. LRP – outcome: continence.
in this review limits any notion of conducting sensitivity analyses to determine the effect of such confounding variables.

**Conclusion**

This systematic review is the first of its kind to summarize evidence from RCTs with respect to the effectiveness of RALP and LRP in the treatment of localized prostate cancer. Given the limited number of RCTs published and the varying quality of existing studies, there is insufficient evidence to wholeheartedly support, or refute, the use of one technique over the other in the treatment of localized prostate cancer. Preliminary results from this level 1 evidence would suggest that RALP is significantly better than LRP at preserving the erectile function and continence. Neither study assessed the impact of surgical experience or volume on outcomes. Further analysis on larger data sets is required to better appreciate what influence factors such as patient age, complications from surgery, surgeon’s experience, surgical volume, clinical pathways and health insurance have upon length of stay [19]. This review supports the call for greater RCTs to identify the gold standard treatment in the field of radical prostatectomy.

**References**