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Permalink
https://escholarship.org/uc/item/28f3v3wg

Journal
BJU International, 112(4)

ISSN
1464-4096

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Publication Date
2013-08-01

DOI
10.1111/j.1464-410X.2012.11493.x

Peer reviewed
How does robot-assisted radical prostatectomy (RARP) compare with open surgery in men with high-risk prostate cancer?

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What's known on the subject? and What does the study add?

• Previous studies have shown that robot-assisted radical prostatectomy (RARP) can be performed in men with high-risk prostate cancer with similar outcomes to that of open surgery. However, most of the literature consists of small case series and compares RARP outcomes to open outcomes from the literature.

• This study compared a cohort of high-risk patients undergoing open RP and RARP at a single institution with good follow up. We found no difference in positive margin rates or likelihood of prostate cancer recurrence. This adds to the growing evidence that RARP is a safe option for men with high-risk disease.

Objective

• To compare oncological outcomes in high-risk patients who underwent open retropubic radical prostatectomy (RRP) and robot-assisted RP (RARP) at a single institution. Despite equivalent oncological outcomes between open RRP and RARP, the use of RARP in men with high-risk tumours has been debated.

Patients and Methods

• A retrospective analysis of high-risk patients treated with open RRP or RARP at UCSF from 2002 to 2011 was conducted.

• The relationship between surgical approach and positive margin rate was assessed by multivariate logistic regression.

• Cox proportional hazards regression assessed the effect of surgical approach on time to tumour recurrence.

Results

• In all, 177 open RRP and 233 RARP patients made up the final cohort for analyses. The mean (SD) age was 61.6 (6.6) years and the median (range) follow-up was 27 (2–112) months.

• RARP patients had less blood loss (median 200 vs 400 mL, P < 0.01) and underwent complete bilateral nerve sparing more often (54% vs 34%, P < 0.01) than those undergoing open RRP.

• There were no differences by approach in pathological grade, stage, or positive margin rates. However, there was a trend towards higher positive margin rates with RARP early on.

• Recurrence-free survival was similar at 2 years (84% and 79%) and 4 years (68% and 66%) after open RRP and RARP, respectively (log-rank P = 0.53).

Conclusions

• This study is novel in that it assesses outcomes of open RRP vs RARP in a cohort of high-risk men at a single institution.

• RARP appears to be a feasible option for men with high-risk prostate cancer and displayed equivalent oncological outcomes compared with open RRP.

Keywords

robotic surgery, high-risk, prostate cancer, outcomes

Introduction

Despite a migration towards the diagnosis of more localised prostate cancer with serum PSA screening [1], 20–30% of patients still present with high-risk, non-metastatic disease [2]. Such patients are candidates for aggressive local and regional therapy including combined radiation and androgen-deprivation therapy (ADT) or...
surgery followed by selective application of adjuvant or salvage secondary therapy. Recently, some have justified an initial surgical approach [3]. This has been supported by contemporary studies that have shown favourable results in treating high-risk disease with radical prostatectomy (RP) [3–7]. A recent comparative effectiveness study assessing >7000 men in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database found that men with high-risk prostate cancer had a lower mortality if they were treated primarily with surgery compared with external-beam radiation or ADT monotherapy [4].

This preference toward the surgical management of high-risk disease overlaps the increasing use of minimally invasive surgery via robot-assisted RP (RARP). This approach has gained popularity due to reported improvements in blood loss and recovery, and equivalent short-term functional and oncological outcomes compared with open retropubic RP (RRP) [8]. As a result, it is becoming the most common approach for prostate cancer surgery in the USA [9]. However, there is limited information on the outcomes of men with high-risk features. Most contemporary studies of RARP in high-risk men, despite short follow-up, have reported outcomes comparable with most open RP series [10,11]. This suggests that RARP may be a feasible option for men with more aggressive disease.

Most of the current literature on RARP for high-risk prostate cancer consists of small descriptive cohort studies looking only at outcomes of robotic surgery with no open group for comparison. Therefore, we sought to compare oncological outcomes of high-risk men undergoing open RP and RARP at the University of California, San Francisco (UCSF), to assess the efficacy of RARP in this population of men.

**Patients and Methods**

Men with high-risk prostate cancer, who were treated with RP, either open RRP or RARP, from 2002 to 2011 at UCSF were selected for this study. Exclusion criteria included men with metastatic disease via imaging at presentation or the use of any neoadjuvant treatments before surgery for prostate cancer. Patients were also excluded if they had <6 months follow-up or two PSA tests after surgery. ‘High risk’ was defined according to the National Comprehensive Cancer Network and referred to men with clinical stage ≥T3a, biopsy Gleason 8–10, or serum PSA levels of >20 ng/mL. Baseline and follow-up demographic and clinical information were extracted from the UCSF Urologic Oncology Database. Both techniques were performed by multiple surgeons. Open RRP was performed in the standard fashion via retrograde dissection of the prostate gland [12]. All patients included in this study provided written informed consent under Institutional Review Board approval for use of their clinical data in research.

Oncological outcomes were assessed by surgical margin status and recurrence-free survival (RFS). Recurrence of prostate cancer was defined as two consecutive PSA values ≥0.2 ng/mL and/or the receipt of any salvage treatments for prostate cancer [13]. Patients receiving secondary therapies were included in the analysis. Adjuvant treatment was defined as treatment for prostate cancer occurring ≤6 months after surgery, while salvage treatments were defined as treatments for recurrent prostate cancer occurring >6 months from surgery.

Baseline and follow-up demographic and clinical characteristics of open RRP and RARP patients were evaluated and compared using chi-square for categorical variables and ANOVA for continuous variables. Kaplan-Meier analysis was used to determine the 2- and 4-year RFS for both open RRP and RARP patients. Multivariate logistic regression was used to assess the likelihood of positive surgical margins in open RRP and RARP patients. Models were adjusted for age at diagnosis, PSA level at diagnosis, pathological T-stage, lymph node involvement, type of nerve sparing procedure, year of surgery and surgeon. Nerve sparing was categorised as either none, partial/unilateral or complete bilateral. Pathological stage was dichotomised into T2 and T3/T4. A significant interaction was found between surgical approach and year of surgery, dichotomised into before or after 2006. Therefore, odds ratios (ORs) and 95% CIs for the likelihood of positive margins were reported separately for patients undergoing surgery from 2002 to 2006 and 2007 to 2011. ORs are reported for robotic surgery using RRP patients as a reference group.

Cox proportional hazards regression models were used to assess the probability of recurrence among RRP and RARP patients. This analysis was adjusted for similar covariates as well as surgical margin status and receipt of secondary treatments. There was no significant interaction between surgical approach and time of surgery. Secondary treatments were defined either as none, radiation, ADT or both. Hazard ratios (HRs) and 95% CIs are reported for the likelihood of cancer recurrence in RARP patients using RRP patients as a reference.

A sensitivity analysis was performed using a definition of any single PSA level of >0.05 ng/mL and/or the receipt of any salvage treatment for prostate cancer to define recurrence. This analysis was restricted to patients who had hypersensitive assays used for PSA detection.

**Results**

Among the 3643 patients with prostate cancer in our institutional database who consented for research, 555 were
Patients in Urological Oncology Database in 2011 n = 3887

Consented for research n = 3643

NCCN high risk at diagnosis n = 704

Treated with open or robot assisted radical prostatectomy since 2002 n = 555

No neoadjuvant treatments; at least 2 PSAs or 6 months follow up n = 410

Open radical prostatectomy n = 177 (43%)

Robot-assisted laparoscopic prostatectomy n = 233 (57%)

Fig. 1 Patient flow chart.

Table 1 Patients’ demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>RRP</th>
<th>RARP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age at diagnosis, years N (%)</td>
<td>60.8 (6.38)</td>
<td>61.3 (6.78)</td>
<td>0.50*</td>
</tr>
<tr>
<td>Race/ethnicity:</td>
<td></td>
<td></td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>7 (4)</td>
<td>24 (11)</td>
<td></td>
</tr>
<tr>
<td>Latino</td>
<td>1 (1)</td>
<td>3 (1)</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>4 (2)</td>
<td>10 (4)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>154 (87)</td>
<td>192 (82)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>11 (6)</td>
<td>4 (2)</td>
<td></td>
</tr>
<tr>
<td>PSA level, ng/mL:</td>
<td></td>
<td></td>
<td>0.50†</td>
</tr>
<tr>
<td>≤4</td>
<td>19 (11)</td>
<td>35 (15)</td>
<td></td>
</tr>
<tr>
<td>4.1–10</td>
<td>109 (62)</td>
<td>137 (59)</td>
<td></td>
</tr>
<tr>
<td>10.1–20</td>
<td>29 (16)</td>
<td>31 (13)</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>20 (11)</td>
<td>30 (13)</td>
<td></td>
</tr>
<tr>
<td>Clinical T-stage:</td>
<td></td>
<td></td>
<td>0.43†</td>
</tr>
<tr>
<td>T1</td>
<td>59 (33)</td>
<td>92 (39)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>116 (66)</td>
<td>139 (60)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Biopsy Gleason grade:</td>
<td></td>
<td></td>
<td>0.38†</td>
</tr>
<tr>
<td>2–6</td>
<td>8 (5)</td>
<td>8 (3)</td>
<td></td>
</tr>
<tr>
<td>7 (3 + 4)</td>
<td>5 (3)</td>
<td>8 (3)</td>
<td></td>
</tr>
<tr>
<td>7 (4 + 3)</td>
<td>59 (33)</td>
<td>61 (27)</td>
<td></td>
</tr>
<tr>
<td>8–10</td>
<td>105 (59)</td>
<td>156 (67)</td>
<td></td>
</tr>
<tr>
<td>% cores positive on biopsy:</td>
<td></td>
<td></td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>&lt;33</td>
<td>46 (29)</td>
<td>76 (34)</td>
<td></td>
</tr>
<tr>
<td>33–66</td>
<td>55 (35)</td>
<td>100 (45)</td>
<td></td>
</tr>
<tr>
<td>&gt;66</td>
<td>58 (36)</td>
<td>48 (21)</td>
<td></td>
</tr>
<tr>
<td>Year of surgery:</td>
<td></td>
<td></td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>&lt;2006</td>
<td>107 (60)</td>
<td>7 (3)</td>
<td></td>
</tr>
<tr>
<td>≥2006</td>
<td>70 (40)</td>
<td>226 (97)</td>
<td></td>
</tr>
</tbody>
</table>

*t-test; †chi-square test.

diagnosed with high-risk disease and treated with either open RRP or RARP since 2002. After exclusion of patients treated with neoadjuvant therapy or with inadequate follow-up, 410 men comprised the final cohort. Among these men, 177 (43%) were treated with RRP while 233 (57%) were treated with RARP. Figure 1 shows the flow chart for the selection of study patients. The mean follow-up was 48 months and 22 months in the open RRP and RARP group, respectively. Within 4 years, 49 men recurred in the RRP group of which 26 were due to PSA failure (53%), while 32 recurred in the RARP group of which 22 (69%) were due to PSA failure.

Baseline demographic and clinical information for patients are shown in Table 1. The RARP patients differed from RRP patients in race/ethnicity and year of surgery (both P < 0.01), with most of the RARP patients having their surgery after 2006 compared with RRP patients of whom most had their surgery before 2006. The mean percentage of positive biopsy cores was lower in RARP patients than the RRP patients. The distribution of Cancer of the Prostate Risk Assessment (CAPRA) scores appeared similar between the open RP and RARP groups (Fig. 2). Perioperative and pathological information at the time of surgery is given in Table 2. RRP patients had a longer hospital stay, more blood loss and a higher transfusion rate than RARP patients, as expected (all P < 0.01). More men undergoing RARP had complete nerve sparing procedures (54% vs 34%) and fewer had no nerve sparing (2% vs 8%), compared with those undergoing RRP (P < 0.01). There were no statistically significant differences in pathological tumour staging, Gleason grading, tumour volume or rates of extracapsular extension or seminal vesicle involvement between the open RRP and RARP patients. The positive margin rate was not significantly different between the RRP
and RARP (68/233 [29%]) patients ($P = 0.13$). RARP patients had fewer lymphadenectomies (63% vs 96%, $P < 0.01$) and less lymph node involvement (4% vs 15%, $P < 0.01$). Lymph node yield also was lower in RARP patients than in RRP patients (11 vs 15, $P < 0.01$). Adjuvant therapy was given in 13% of RRP patients vs 5% of RARP patients, while salvage therapy was given in 18% of RRP patients compared with 6% of RARP (Table 2).

Multivariate logistic regression showed an increased trend toward more positive margins with RARP ($P = 0.05$) in patients who had their surgery before 2006 but no difference in the likelihood of positive margins by surgical approach in men who had their surgery after 2006 (Table 3). There was no effect of pathological Gleason score on margin status, although higher pathological T-stage and PSA level appeared to predict an increased likelihood of positive margins.

RFS for RARP compared with RRP was 84% vs 79% at 2 years and 68% vs 66% at 4 years (log-rank $P = 0.52$; Fig. 3). There was no appreciable difference between RRP and RARP patients. Cox proportional hazards regression looking at predictors of tumour recurrence are shown in Table 4. There did not appear to be any difference in the probability of recurrence between RARP and open RRP.

Finally, we performed a sensitivity analysis using any PSA level $>0.05$ ng/mL to define prostate cancer recurrence, which failed to show a relationship between surgical approach and rates of recurrence (data not shown).

**Discussion**

Recently there has been a trend towards favouring surgery in the treatment of men with high-risk prostate cancer [4]. Although the open RRP has been the standard for prostate cancer surgery, the robot-assisted technique has gained in popularity and shown similar oncological and functional outcomes to open surgery [14,15]. However, its use in the setting of high-risk tumours is unclear. To help address these concerns, men with high-risk prostate cancer undergoing open RRP and RARP at UCSF were assessed to compare outcomes. Men undergoing RARP were found to have a shorter hospital stay and less blood loss than men undergoing open RRP. For oncological outcomes, positive margin rates and progression-free survival appeared similar between the two groups.
**Table 3** Multivariate logistic regression comparing likelihood of positive margin by surgical approach.

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robotic vs open† (2002–2006)</td>
<td>0.43 (0.24–0.75)</td>
<td>0.01</td>
</tr>
<tr>
<td>Robotic vs open† (2006–2011)</td>
<td>0.64 (0.29–1.41)</td>
<td>0.27</td>
</tr>
<tr>
<td>PSA level†</td>
<td>1.03 (1.00–1.05)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pathological Gleason§ (≤G3 + 4 vs ≥G4 + 3)</td>
<td>0.98 (0.57–1.68)</td>
<td>0.94</td>
</tr>
<tr>
<td>Pathological T-stage¶ (T3/4 vs T2)</td>
<td>4.39 (2.57–7.50)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Outcome of positive surgical margin given as OR (95% CI) using logistic regression. Analysis adjusted for age at diagnosis, lymph node status, surgeon, and nerve sparing procedure. OR for likelihood of positive surgical margin given for robotic approach using open approach as reference. OR for likelihood of positive margin for each one unit increase in PSA level. OR for likelihood of positive surgical margin given for Gleason ≤3 + 4 using Gleason ≥4 + 3 as a reference. OR for likelihood of positive surgical margin given for pathological T3/4 using T2 as a reference.

Despite a significant increase in the use of RARP for the surgical management of prostate cancer, previous studies have criticised its use, stating that complications and positive margin rates are too high [16]. However, such findings may be due largely to early experience with this new technology while surgeons are still on their learning curve. Studies have shown that greater surgical volume and experience lead to better outcomes [17] and robotic surgery is not likely an exception to this rule. The present study supports the effect of surgical volume on improved outcomes, as seen by the trend towards increased positive margins in the infancy of RARP at our institution compared with similar margin rates between open and robotic approaches in more contemporary patients. Investigators assessing outcomes at high-volume centres have reported similar oncological and functional outcomes between open and robot-assisted techniques [14,15]. As a result RARP is becoming the most popular approach for the surgical management of localised prostate cancer and is increasingly being used for men with higher-risk disease.

The present findings of shorter hospital stays and less blood loss with RARP than open RRP have been reported in other studies [8], and are some of the reasons why this technique has gained in popularity. For pathological endpoints we found higher rates of pathological T-stage, Gleason grade, and extracapsular extension among RRP patients compared with RARP patients, but none of these were statistically significant. However, there were fewer patients with lymph metastases in the RARP group than in the open RRP group. Furthermore, the number of patients who received a lymph node dissection was significantly lower in the RARP group compared with those undergoing open RRP. This was concerning given the high-risk characteristics of these patients. Studies have suggested that for men with moderate- or high-risk disease an extended lymph node dissection provides a diagnostic and perhaps even a therapeutic benefit [18,19]. However, the present findings are consistent with other studies that have shown a higher likelihood of receiving a lymph node dissection in patients undergoing an open procedure compared with a robotic one [20]. Despite concerns about the ability to perform an adequate lymph node dissection via a robotic technique, most contemporary series have reported equivalent outcomes and lymph node yields between open and robotic approaches [21]. Lower rates of lymph node dissections and nodal yields in the RARP group in the present study may have been secondary to the learning curve of robotic surgery in its early use. This is supported by an increase in the rate of lymphadenectomy in RARP patient’s from 15% in 2005 to 73% by 2011. The mean lymph node yield appeared stable over time.

In the present series, more men treated with RARP had a complete bilateral nerve sparing procedure, while more men undergoing open RRP had a non-nerve sparing procedure. It is not clear whether the robotic approach improved the ability to perform a nerve sparing procedure or whether a nerve sparing procedure was attempted more
in the robotic approach due to the expectation of the men receiving it. Furthermore, there may have been a perception of lower risk of extracapsular extension based on lower tumour volume on biopsy and a trend towards lower clinical T-stage in the RARP group. In addition, the increased use of MRI in the more contemporary patients, who underwent RARP, may have led to increased nerve sparing in these patients, if they were found to have organ-confined disease regardless of Gleason score or other clinical risk parameters. Despite a significant risk of extracapsular extension in both groups, we failed to find a difference in positive margin status between the two techniques suggesting that inappropriate nerve sparing was not being performed. In addition, it is likely that nerve preservation was incremental in nature from no sparing, to partial sparing and finally complete sparing.

The present findings of similar oncological outcomes between high-risk patients treated with either open or robotic surgery are comparable with other reports. Jayram et al. [22] published a study of 148 men with high-risk prostate cancer treated with RARP and reported a positive margin rate of 20% and a biochemical recurrence rate of 21% over 2 years. Similarly, a study of 69 men aged >70 years with high-risk prostate cancer reported a biochemical RFS of 91% at 12 months and 86% at 36 months [10]. These outcomes are comparable with those reported in open RP series for high-risk tumours, where positive margin rates range from 18% to 57% and 5- to 10-year biochemical RFS ranges from 56% to 80% [6,23–25]. Support for this finding is presented by Wambi et al. [11], who studied 368 high-risk men treated with RARP from various centres and found equivalent biochemical RFS outcomes compared with men treated with open RP. These reports, along with our own, support the finding that RARP can be performed in men with high-risk disease with equivalent oncological results as open RP.

The strengths of the present study included a relatively large sample of men with high-risk cancer features treated with both open and robotic approaches at the same institution. In addition, we were able to assess both pathological and oncological outcomes with complete follow-up. The present study had some limitations, which should be noted. Firstly, RRP and RARP patients appeared to differ in the timing of their treatments with RRP patients primarily being treated before 2006 and RARP patients being treated after 2006. Although this difference in timing may have affected the outcome, we restricted the analysis to patients treated within the last decade to minimise this bias and we also adjusted for the year of surgery. Secondly, positive margin status and the likelihood of prostate cancer recurrence provided assessments of oncological control. However, not all patients who have a positive margin or recurrence will progress or die from prostate cancer.

Although mortality outcomes may be more meaningful we were unable to assess this, as only four men died in the present study making it underpowered to assess mortality outcomes. In addition, the mean follow-up in the open and robotic arms was 4 and 2 years, respectively. We tried to minimise such a difference by using both PSA level and second treatment endpoints. We also performed a sensitivity analysis using a PSA level of ≥0.05 ng/mL to define prostate cancer recurrence, which failed to show any significant effect of surgical approach on recurrence rates. Longer follow-up in the robotic arm may affect recurrence outcomes seen in this analysis. Finally, there may be some heterogeneity among men in this cohort defined as ‘high risk’. However, CAPRA scores appeared similar between the open and robotic groups suggesting that the groups were well balanced in risk assessment.

In conclusion, we found no difference in pathological and oncological outcomes in patients treated with either RARP or open RRP for high-risk prostate cancer at a single, high-volume institution. Therefore, as more men with high-risk prostate cancer move towards surgery, the choice to use an open vs robotic approach should depend on the surgeon and their level of comfort and experience with each approach.

**Conflict of Interest**

None declared.

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Abbreviations: ADT, androgen-deprivation therapy; CAPRA, Cancer of the Prostate Risk Assessment; CaPSURE, cancer of prostate strategies and urologic research endeavors; HR, hazard ratio; OR, odds ratio; RFS, recurrence-free survival; (RA)(R)RP, (robot-assisted) (retropubic) radical prostatectomy; UCSF, University of California, San Francisco.