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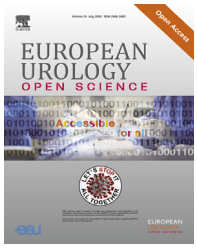

European Association of Urology

Prostate Cancer

Risk of Recurrent Disease 6 Years After Open or Robotic-assisted Radical Prostatectomy in the Prospective Controlled Trial LAPPRO

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Abstract

Background: Conclusive evidence of superiority in oncological outcome for robot-assisted laparoscopic prostatectomy (RALP) over retropubic radical prostatectomy (RRP) is lacking.
Objective: To compare RALP and RRP regarding recurrent disease and to report the mortality rate 6 yr after surgery.
Design, setting, and participants: A total of 4003 men with localized prostate cancer were enrolled between 2008 and 2011 in Laparoscopic Prostatectomy Robot Open (LAPPRO)— a prospective, controlled, nonrandomized trial performed at 14 Swedish centers.
Outcome measurements and statistical analysis: Data were collected at visits and by patient questionnaires at 3, 12, and 24 mo, and through a structured telephone interview at 6 yr. Cause of death was retrieved from the National Cause of Death Register in Sweden. The modified Poisson regression approach was used for analyses.
Results and limitations: After adjustment for patient-, tumor-, and surgeon-related confounders, no statistically significant difference was observed between RALP and RRP in biochemical recurrence rate (14 vs 16%, relative risk [RR] 0.77, 95% confidence interval [CI] 0.56–1.06) or in not cured endpoint (22% vs 23%, RR 0.82, 95% CI 0.6–1.11).

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Stratified by D'Amico risk group, a significant benefit for RALP existed for recurrent disease in high-risk patients (RR 0.47, 95% CI 0.26–0.86, $p = 0.02$). All-cause mortality was 3% ($n = 96$). Prostate cancer–specific mortality was 0.6% ($n = 21$) overall, 0.3% ($n = 8$) after RALP, and 1.5% ($n = 13$) after RRP. The nonrandomized design is a limitation.

Conclusions: No significant difference was observed for cancer recurrence rate between RALP and RRP 6 yr after surgery. However, in a subgroup analysis, we found a significant benefit for RALP regarding recurrence rate in the high-risk group. Larger studies with longer follow-up are needed to make a firm conclusion and to evaluate a possible survival benefit.

Patient summary: In general, the oncological outcome is comparable between robotic and open radical prostatectomy 6 yr after surgery. For high-risk patients, our findings indicate that there is an advantage for robotics, but further studies with longer follow-up time is needed to make a firm conclusion.

1. Introduction

Localized prostate cancer is often treated by radical prostatectomy. The long-term outcome of radical prostatectomy with 29-yr follow-up time has been reported from the randomized Scandinavian Prostate Cancer Group trial 4 (SPCG-4), with a reduction in prostate cancer mortality and 2.9 life years gained in comparison with "watchful waiting" in favor of radical prostatectomy [1]. However, long-term complications from the operation such as urinary incontinence and erectile dysfunction are severely impacting quality of life in many patients [2–5]. Thus, the surgical procedure should balance the long-term oncological benefits against functional outcomes [6].

In SPCG-4, the intervention tested was open retropubic radical prostatectomy (RRP). Later, robot-assisted laparoscopic prostatectomy (RALP) was introduced and rapidly established as a standard procedure at many centers. However, long-term benefits with the robotic procedure compared with open surgery have not been demonstrated convincingly, and this far, only one randomized trial comparing RALP and RRP has been published [7]. Our prospective, controlled, nonrandomized trial, Laparoscopic Prostatectomy Robot Open (LAPPRO), with a multicenter design compared RALP and RRP and reported a small but statistically significant benefit in erectile dysfunction at 1 and 2 yr favoring RALP, but with no significant difference regarding incontinence [5,6]. At 2-yr follow-up, there was no significant difference regarding recurrence rate [6].

Here, we report oncological outcome and death rates 6 yr after surgery for prostate cancer comparing RALP and RRP in the LAPPRO trial.

2. Patients and methods

2.1. Study design and participants

The LAPPRO trial has been described in detail previously [8]. In brief, LAPPRO is a prospective, controlled, nonrandomized trial comparing RALP and RRP. Enrollment took place between September 2008 and November 2011 at 14 Swedish departments of Urology, with seven performing RRP and seven RALP. Analyses included patients with the following criteria: age <75 yr, clinical tumor stage ≤T3, prostate-specific antigen (PSA) concentration at diagnosis <20 ng/ml, and no signs of distant metastasis. Clinical information was collected by health care personnel in case report forms (CRFs) before and during operation, as well as during hospital stay and 3, 12, and 24 mo after surgery. Patients answered four printed questionnaires before the operation and at 3, 12, and 24 mo postoperatively. Six years after radical prostatectomy, patients answered a structured telephone interview with 14 questions including PSA values, radiotherapy, and pharmacological treatments. Information on PSA, salvage or adjuvant treatment, disease progression, and metastatic spread was collected at follow-up and reported in CRFs (at 3, 12, and 24 mo) and at the telephone interview 6 yr after surgery. Telephone interviews were performed by a research nurse without access to individual patient data from the LAPPRO study. Date of death and cause of death were retrieved from the National Cause of Death Register (National Board of Health and Welfare) of Sweden. The study was approved by the Regional Ethical Review Board in Gothenburg (No 277-07) and registered in the Current Controlled Trials database (ISRCTN 06393679).

2.2. Outcome measurements and definitions

The primary objective was to compare RALP with RRP regarding the rate of residual and recurrent disease 6 yr after surgery as treatment for localized prostate cancer. We used the same endpoint definitions as previously published [6]. *Residual disease* was defined as a PSA value of >0.25 ng/ml at first postoperative measurement (6–12 wk after surgery).

Biochemical recurrence (BCR) was defined as a PSA value of <0.25 ng/ml at 6–12 wk after surgery, followed by a PSA value of >0.25 ng/ml at 1, 2, or 6 yr with a repeated value at the same or a higher level. The combined endpoint *not cured* consists of residual disease, BCR, adjuvant or salvage treatment, metastatic disease, and/or death of prostate cancer. *Treatment* was defined as adjuvant or salvage radiotherapy, chemotherapy, or hormonal therapy (antiandrogens or castration therapy by surgery or gonadotropin-releasing hormone [GnRH], and GnRH agonist/antagonist), and was reported separately.

Secondary objectives were to analyze risk factors for residual and recurrent disease and to report the rate of prostate cancer–specific and all-cause mortality at 6 yr after the operation.

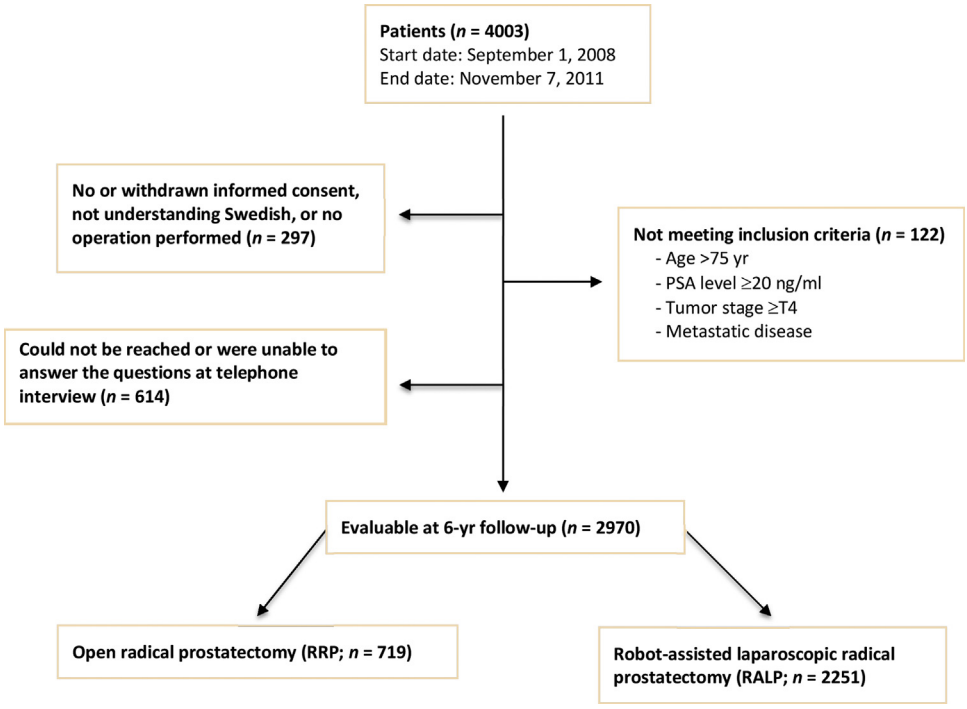

Fig. 1 – Flow chart—enrollment. Numbers may not sum properly, as the same participant may have fulfilled more than one exclusion criterion. PSA = prostate-specific antigen; RALP = robot-assisted laparoscopic prostatectomy; RRP = retropubic radical prostatectomy.

In accordance with earlier LAPPRO reports, we performed subgroup analyses on patients operated by surgeons with stated experience of > 100 radical prostatectomies before entering the trial [5,6] and on D'Amico risk groups [9].

2.3. *Statistical analysis*

A statistical analysis plan was specified before the dataset was opened for analyses. The sample size for LAPPRO was originally derived to assess the primary outcome: urinary incontinence at 12-mo follow-up. In this study, we used the modified Poisson regression approach of Zou [10] with robust variance estimation, log-link, and surgeon as clustering variables to account for intrasurgeon dependency to analyze primary and secondary outcomes. For the primary objective, preoperative PSA level, prostate weight, pathological T stage, prostatectomy Gleason score, as well as surgeon annual volume during the study period and surgeon prior experience (total number of either RALP or RRP before the current procedure) were included as covariates for confounding adjustment. In the risk factor assessment, the variables considered were the same as adjusted for in the primary analysis and also surgical margin status, and involved simple and multiple regressions. No imputation of missing values or correction for multiplicity was performed. We used SAS v.9.4 for Windows (SAS Institute Inc., Cary, NC, USA) for statistical analysis.

3. Results

The LAPPRO trial enrolled a total of 4003 patients, and 3584 of them fulfilled the specific criteria to be included in the current analyses (Fig. 1). After the telephone interviews at 6 yr, 614 patients were excluded as they could not be reached or were unable to answer the questions. The resulting cohort consisted of 2970 patients. For the subgroup analysis of experienced surgeons, 2178 patients were identified.

Patient, tumor, and surgeon characteristics are shown in Table 1. The distribution of baseline characteristics (age, educational level, marital status, and comorbidities) was similar among patients operated by RRP and RALP. The same was true regarding tumor characteristics (preoperative PSA level, prostate weight, pathological T stage, prostatectomy Gleason score, and positive surgical margin status). The 2970 prostatectomies were performed by 80 surgeons, 31 performing RALPs and 49 performing RRPs. Robotic surgeons had less prior experience than open surgeons, but had a higher annual volume during the study period (Table 1). Radiotherapy after surgery was given to 14% ($n = 325$) of those operated by RALP and 14% ($n = 99$) of those operated by RRP, and the corresponding values were, respectively, 1% ($n = 30$) and 1% ($n = 5$) for chemotherapy, and 7% ($n = 160$) and 9% ($n = 60$) for hormonal therapy. Metastatic disease was reported by 1% in both groups ($n = 31$ for RALP, $n = 10$ for RRP). Only 0.1% ($n = 3$) versus 0.6% ($n = 4$) reported that they had undergone surgical orchidectomy.

The oncological outcomes are presented in Table 2. The rate of not cured patients was 22% after RALP and 23% after RRP. For BCR and the combined endpoint not cured, no significant difference was observed between RALP and RRP. There was a statistically significant lower risk for residual disease after RALP when adjustments for surgeon annual volume and prior experience were included in the models (adjustment B).

When analyses were performed only for patients operated by surgeons with stated experience of > 100 radical prostatectomies before entering the trial, there were no significant differences between RALP and RRP

Table 1 – Patient, tumor, and surgeon characteristics

Variable	Category	RALP (*n* = 2251)	RRP (*n* = 719)	All (*n* = 2970)
Age	Median (Q1; Q3)	64.0 (59.0; 67.0)	64.0 (60; 68)	63.1 (59.0; 64.0)
Marital status	Living w partner	1698 (84.7)	539 (85.1)	2237 (85.1)
	Living w/o partner	306 (15.3)	86 (13.8)	392 (14.9)
	Missing	247	94	341
Education	Not university	1224 (61.1)	410 (65.5)	1634 (62.1)
	University	781 (38.9)	216 (34.5)	997 (37.0)
	Missing	246	93	339
Residence	City	951 (47.5)	192 (30.7)	1143 (43.5)
	Rural	271 (13.5)	115 (18.4)	386 (14.7)
	Village/town	777 (38.8)	318 (50.9)	1095 (41.7)
	Abroad	5 (0.25)		5 (0.19)
	Missing	247	94	341
Comorbidity[a]	Yes	1012 (50.3)	328 (52.2)	1340 (50.8)
	No	1002 (49.8)	300 (47.8)	1302 (49.2)
	Missing	237	91	328
Pathology T stage	T2	1605 (73%)	520 (74%)	2125 (73%)
	T3	583 (27%)	176 (25%)	759 (26%)
	T4	10 (0.5%)	3 (0.4%)	13 (0.4%)
	Missing	53	20	73
Pathology Gleason score	≤7	2074 (94%)	668 (95%)	2742 (94%)
	>7	143 (6%)	33 (5%)	176 (6%)
	Missing	34	18	52
Preop PSA (ng/ml)	0–4.4	548 (24%)	172 (25%)	722 (24%)
	4.5–6.1	596 (27%)	168 (24%)	764 (26%)
	6.2–9.1	588 (26%)	188 (27%)	776 (26%)
	≥9.2	516 (23%)	178 (25%)	694 (23%)
	Missing	3	11	14 (0.5%)
Preop PSA (ng/ml)	0–10	1842 (82%)	566 (80%)	2409 (81%)
	10-20 ng/ml	405 (18%)	142 (20%)	547 (19%)
	Median (Q1;Q3)	6.1 (4.5; 8.9)	6.3 (4.5; 9.2)	6.1 (4.5; 9.0)
	Missing	3	11	14
Prostate weight (g)	0–19	20 (0.9%)	3 (0.4%)	23 (0.8%)
	20–39	900 (40%)	240 (34%)	1140 (38%)
	40–59	944 (42%)	314 (45%)	1258 (43%)
	60–79	263 (12%)	94 (13%)	357 (12%)
	≥80	103 (5%)	46 (7%)	149 (5%)
	Missing	21	22	43
Surgical margin status	Negative	1721 (78%)	533 (76%)	2254 (76%)
	Positive	464 (21%)	149 (21%)	613 (21%)
	Not stated	28 (1%)	16 (2%)	44 (1%)
	Missing	38	21	59
D'Amico risk groups, n (%)	High	177 (8)	57 (8)	234 (8)
	Intermediate	1398 (63)	423 (61)	1821 (62)
	Low	648 (29)	214 (31)	862 (30)
	Missing	28	25	53
Surgical margin status by D'Amico risk groups	**High**			
	Negative	134 (78%)	35 (63%)	169 (72%)
	Positive	33 (19%)	18 (32%)	51 (22%)
	Intermediate			
	Negative	1076 (78%)	314 (76%)	1390 (76%)
	Positive	288 (21%)	91 (22%)	379 (21%)
	Low	491 (77%)	175 (83%)	666 (77%)
	Negative			
	Positive	136 (21%)	34 (16%)	170 (20%)
Surgeon caseload during LAPPRO	Median (Q1; Q3)	60 (38; 77)	28 (14; 80)	45 (29; 77)
Surgeon prior experience	Median (Q1; Q3)	161 (81; 28.3)	513 (128; 1146)	178 (94; 352)

COPD = chronic obstructive pulmonary disease; LAPPRO = Laparoscopic Prostatectomy Robot Open; PSA = prostate-specific antigen; W = with; w/o = without.
[a] Comorbidity is defined as responding "yes" to at least one of questions regarding stroke, thrombosis, neurological disease, diabetes, hypertension, myocardial infarction, angina, heart failure, COPD, gastric ulcer, kidney disease, depression, inguinal hernia, or prostatitis.

in residual disease, BCR, or the combined endpoint not cured (Table 2).

Oncological outcomes by D'Amico risk classification are shown in Table 3. A statistically significant advantage for RALP was observed in the high-risk group for both BCR and not cured groups, while no significant differences were seen in the intermediate- and low-risk groups.

Among preoperative factors used in risk classification, Gleason score (biopsy) and PSA level before surgery were found to be significantly associated with residual and

Table 2 – Oncological outcome at 6-yr follow-up

	Unadjusted analyses				Adjustment A		Adjustment B	
	RALP	RRP	RR (95% CI)	*p* value	RR (95% CI)	*p* value	RR (95% CI)	*p* value
All patients								
Residual disease[a]	37/1504 (2)	13/596 (2)	1.13 (0.66; 1.93)	0.7	0.97 (0.55; 1.72)	0.9	0.69 (0.31; 1.55)	0.4
Missing	41	37			129		192	
BCR[b]	218/1538 (14)	98/631 (16)	0.91 (0.72; 1.16)	0.5	0.89 (0.65; 1.21)	0.5	0.86 (0.57; 1.29)	0.5
Missing	7	2			88		151	
Not cured[c]	334/1492 (22)	131/611 (21)	1.04 (0.76; 1.43)	0.8	0.97 (0.71; 1.32)	0.9	0.86 (0.56; 1.33)	0.5
Missing	53	22			156		218	
Experienced surgeons								
Residual disease[a]	51/2203 (2)	19/681 (3)	0.83 (0.51; 1.36)	0.5	0.75 (0.45; 1.26)	0.3	0.46 (0.23; 0.93)	0.03
Missing	48	38			166		236	
BCR[b]	321/2244 (14)	113/717 (16)	0.91 (0.73; 1.12)	0.4	0.93 (0.71; 1.23)	0.6	0.77 (0.56; 1.06)	0.1
Missing	7	2			121		191	
Not cured[c]	483/2174 (22)	157/687 (23)	0.99 (0.75; 1.3)	0.9	0.96 (0.73; 1.25)	0.8	0.82 (0.6; 1.11)	0.2
Missing	77	22			210		279	

BCR = biochemical recurrence; CI = confidence interval; PSA = prostate-specific antigen; RALP = robot-assisted laparoscopic prostatectomy; RR = relative risk; RRP = retropubic radical prostatectomy.
Adjustment A: pathology T stage, pathology Gleason score, preoperative PSA level, pathology prostate weight.
Adjustment B: same as adjustment A plus surgeon annual volume and surgeon prior experience.
[a] PSA > 0.25 ng/ml at 3 mo.
[b] PSA < 0.25 ng/ml at 3 mo and PSA > 0.25 ng/ml at 1, 2, or 6 yr of follow-up.
[c] PSA > 0.25 ng/ml at any time or radiotherapy, chemotherapy, or hormone therapy at 1, 2, or 6 yr of follow-up.

Table 3 – Oncological outcome by D'Amico risk classification

	Unadjusted analyses				Adjustment A		Adjustment B	
	RALP	RRP	RR (95% CI)	*p* value	RR (95% CI)	*p* value	RR (95% CI)	*p* value
D'Amico high risk								
Residual disease[a]	7/172 (4)	8/51 (16)	0.26 (0.09; 0.72)	0.01	0.27 (0.11; 0.68)	0.005	0.15 (0.02; 1.14)	0.07
BCR[b]	53/176 (30)	18/56 (32)	0.94 (0.55; 1.6)	0.8	0.96 (0.56; 1.63)	0.9	0.33 (0.15; 0.74)	0.01
Not cured[c]	73/173 (42)	28/56 (50)	0.84 (0.55; 1.30)	0.4	0.86 (0.60; 1.24)	0.4	0.47 (0.26; 0.86)	0.02
D'Amico intermediate risk								
Residual disease[a]	36/1372 (3)	11/403 (3)	0.96 (0.49; 1.89)	0.9	0.82 (0.39; 1.72)	0.6	0.52 (0.26; 1.02)	0.057
BCR[b]	214/1395 (15)	66/422 (16)	0.98 (0.74; 1.29)	0.9	1.00 (0.78; 1.28)	1	0.83 (0.59; 1.17)	0.3
Not cured[c]	324/1353 (24)	95/412 (23)	1.04 (0.83; 1.31)	0.7	1.00 (0.78; 1.28)	1	0.80 (0.59; 1.1)	0.2
D'Amico low risk								
Residual disease[a]	7/633 (1)	0/209 (0)	–	–	–	–	–	
BCR[b]	51/645 (8)	24/214 (11)	0.71 (0.43; 1.15)	0.2	0.72 (0.43; 1.19)	0.2	0.61 (0.31; 1.2)	0.2
Not cured[c]	78/621 (13)	28/204 (14)	0.92 (0.59; 1.41)	0.7	0.89 (0.56; 1.41)	0.6	0.79 (0.45; 1.41)	0.4

BCR = biochemical recurrence; CI = confidence interval; PSA = prostate-specific antigen; RALP = robot-assisted laparoscopic prostatectomy; RR = relative risk; RRP = retropubic radical prostatectomy.
Adjustment A: pathology T stage, pathology Gleason score, preoperative PSA level, pathology prostate weight.
Adjustment B: same as adjustment A plus surgeon annual volume and surgeon prior experience.
[a] PSA > 0.25 ng/ml at 3 mo.
[b] PSA < 0.25 ng/ml at 3 mo and PSA > 0.25 ng/ml at 1, 2, or 6 yr of follow-up.
[c] PSA > 0.25 ng/ml at any time or radiotherapy, chemotherapy, or hormone therapy at 1, 2, or 6 yr of follow-up.

recurrent disease, as were postoperative T stage and surgical margin status (Table 4).

Six years after surgery, all-cause mortality was 3% ($n = 96$) and prostate cancer–specific mortality was 0.6% ($n = 21$) in the total cohort of 3584 patients. After RALP, eight of 2698 (0.3%) had died of prostate cancer and 13 of 886 (1.5%) after RRP.

4. Discussion

In this large, prospective trial with 6 yr of follow-up, no statistically significant difference was observed between RALP and RRP regarding recurrent disease at 6 yr. For residual disease, we found a statistically significant advantage for RALP over RRP when analyses included adjustments for surgeon volume–related factors. In a subgroup analysis, stratified by D'Amico risk group, a significantly lower recurrence rate was observed after RALP in the high-risk group, while RALP and RRP were comparable in the other risk groups.

The only randomized controlled trial (RCT) this far comparing BCR rates after RRP and RALP, by Coughlin et al [7], showed a difference in favor of RALP (3% vs 9%) at 24 mo after surgery. However, the authors recommended caution in interpretation of the oncological outcome due to the lack of standardization in postoperative management between

Table 4 – Risk factors for residual and recurrent disease at 6-yr follow-up

		Residual disease[a]		Not cured[b]			
		Unadjusted		Unadjusted		Adjusted[c]	
		RR (95% CI)	*p* value	RR (95% CI)	*p* value	RR (95% CI)	*p* value
Surgical technique	RALP vs RRP	0.83 (0.51; 1.36)	0.5	0.99 (0.75; 1.3)	0.9	0.96 (0.74; 1.23)	0.7
Pathology Gleason score	>7 vs ≤7	4.19 (2.29; 7.66)	<0.001	2.74 (2.27; 3.31)	<0.001	1.73 (1.46; 2.05)	<0.001
Pathology T stage	T3 vs T1 or T2	3.8 (2.08; 6.95)	<0.001	2.83 (2.32; 3.45)	<0.001	1.97 (1.63; 2.39)	<0.001
Preop PSA (ng/ml)	<10 vs 10–20	0.46 (0.29; 0.73)	0.001	0.55 (0.48; 0.63)	<0.001	0.68 (0.57; 0.82)	<0.001
Prostate weight (g)	≤39 vs >40	1.28 (0.85; 1.91)	0.2	1.19 (1.05; 1.35)	0.007	1.20 (1.05; 1.37)	0.01
Surgeon annual caseload	0–49 vs ≥50	0.98 (0.66; 1.46)	0.9	1.1 (0.88; 1.38)	0.4	0.98 (0.79; 1.22)	0.9
Surgeon prior experience	0–100 vs >100	0.87 (0.57; 1.32)	0.5	0.97 (0.8; 1.18)	0.8	1.00 (0.81; 1.23)	1
Surgical margin status	Negative vs positive	0.32 (0.19; 0.51)	<0.001	0.35 (0.30; 0.40)	<0.001	0.46 (0.39; 0.54)	<0.001
Age at surgery (yr)	≤54 vs ≥65	1.19 (0.67; 2.14)	0.6	0.74 (0.6; 0.92)	0.007	0.97 (0.78; 1.2)	0.7
	55–64 vs ≥65	0.67 (0.47; 0.97)	0.03	0.67 (0.59; 0.76)	<0.001	0.82 (0.71; 0.94)	0.006
	≤54 vs 55–64	1.78 (0.96; 3.3)	0.07	1.1 (0.86; 1.41)	0.4	1.18 (0.90; 1.53)	0.2

CI = confidence interval; FU = follow-up; PSA = prostate-specific antigen; RALP = robot-assisted laparoscopic prostatectomy; RR = relative risk; RRP = retropubic radical prostatectomy.

[a] PSA > 0.25 ng/ml at 3 mo.

[b] PSA > 0.25 ng/ml at any time or radiotherapy, chemotherapy, or hormone therapy at 1, 2, or 6 yr of FU.

[c] Surgical technique is adjusted for all other variables in Table 3 except for surgical margin status; surgical margin status is adjusted for all other variables in Table 3 except for surgical technique; the other variables are adjusted for all other variables in Table 3.

the groups and the use of adjuvant treatment. Furthermore, with only one surgeon in each randomization arm, the results are not generally applicable because surgeon heterogeneity was not accounted for. In a recent meta-analysis, Cao and colleagues [11] assessed one RCT and four prospective studies with follow-up time up to 24 mo and found no significant difference in BCR rates between RALP and RRP. Another meta-analysis from 2015, assessing 10 studies published between 2008 and 2015 that compared RALP and RRP with respect to BCR, reported that RALP had better BCR-free survival than RRP (odds ratio 1.33, $p = 0{,}04$) [12]. However, in its sensitivity analysis including only studies with balanced baseline characteristics between trial arms, the results changed significantly, showing no significant difference between methods. In a recent single-center study, Haese et al [13] retrospectively analyzed outcomes among 10 790 men after RALP ($n = 3783$) or RRP ($n = 7007$). No significant difference was observed in 48-mo BCR rate, and surgical approach was not an independent predictor of BCR on multivariable analysis. Another retrospective study by Ritch et al [14] comparing BCR-free survival between RALP and RRP with a median follow-up time from 43 (RRP) to 63 (RALP) mo concluded that the surgical approach did not predict BCR. Taken together, based on the current literature, it is still uncertain whether there is a difference between RALP and RRP regarding recurrent disease, and there is a need for long-term data from large prospective trials.

For the primary objective, we assessed a possible difference in oncological outcome between RALP and RRP at 6 yr of follow-up. We used two sets of adjustment models: first a model with patient- and tumor-related factors (adjustment A) and then a model with additional adjustment for surgeon volume–related factors (adjustment B). Analysis of the entire cohort showed a statistically significant advantage for RALP regarding residual disease only when surgeon volume–related factors were included in the model. Regarding recurrent disease, no significant differences were seen, irrespectively of adjustment. That surgeon experience has an impact on the oncological outcome after RP has previously been reported in learning curve studies by Vickers et al [15,16] for RRP and laparoscopic radical prostatectomy. In a recent single-center study, greater surgeon experience reduced the risk of positive surgical margins after RALP, but not for BCR [17]. The authors suggested further investigation in larger multi-institutional studies, and therefore we consider the results from our prospective, multicenter LAPPRO study to be important. In the current study, we have a difference between RALP and RRP surgeons regarding both prior experience and annual caseload (Table 1), which may explain that adjustment for surgeon volume–related factors had a significant impact on the results.

When analyses were stratified by D'Amico risk group classification, we observed a significant benefit for RALP regarding recurrent disease but only in the high-risk group and when surgeon volume was adjusted for. That the comparison in oncological outcome between methods is dependent on the risk group is in line with a previous publication from the LAPPRO-group at 2-yr follow-up [9]. The advantage for RALP over RRP in high-risk tumors could be related to a higher rate of positive surgical margins for RRP in the high-risk group (Table 1), but is still not fully understood. Since the total number of patients in the high-risk group was rather small (177 for RALP and 57 for RRP), the results should be interpreted with caution and further analyses with longer follow-up time are needed to make a firm conclusion if a difference between surgical techniques really exists among risk groups.

In the second subgroup analysis, we analyzed patients operated by surgeons with prior experience of at least 100 radical prostatectomies. This analysis was performed to

be able to compare the present results with previous LAPPRO reports with shorter follow-up time. In previous reports, at 1 and 2 yr of follow-up, surgeon volume factors were not included in the statistical models. Instead, less experienced surgeons with prior experience of <100 surgeries were excluded. With the same cohort restriction (surgeons with at least 100 prostatectomies), no difference between RALP and RRP was seen in the present report, which is similar to the findings in our 2-yr follow-up publication [6]. The rate of not cured patients at 2 yr after surgery was 13% in both groups, as compared with 22% for RALP and 21% for RRP at 6 yr. This illustrates that a long follow-up time is needed to evaluate accurately oncological outcomes for prostate cancer surgery.

In a secondary analysis, we investigated the risk factors for residual and recurrent disease. As expected, tumor-related factors (PSA, Gleason score, and pathological T stage) were significantly correlated with the rate of both residual and recurrent disease. In previous LAPPRO reports, we have adjusted for tumor-related factors in the regression model, but this is the first time that we were able to show that a correlation really exists. Positive surgical margin status was also significantly associated with an increased risk of residual and recurrent disease.

At 6-yr follow-up, all-cause mortality was 3% (n = 96) in the total cohort and only 21 men died of prostate cancer. Owing to the low number of events, we did not undertake a comparative analysis between RALP and RRP regarding all-cause mortality or prostate cancer–specific survival. Longer follow-up time is needed before reliable analyses can be performed.

Strengths of the present study are the large number of patients included and the high proportion of patients available for analyses. The prospective nature, a multicenter design, and a large number of surgeons enabled the collection of data representing real-life prostate cancer care in Sweden and making the results generalizable. The nonrandomized design is a limitation together with the low number of deaths. Another limitation is the small number of events in subgroup analyses stratified by D'Amico risk groups, making these results somewhat uncertain. We consider the response rate (83%) on the telephone interview at 6 yr after surgery to be fully acceptable, but it is, as expected, lower than in previous LAPPRO reports with shorter follow-up. Owing to differences between laboratories, we used a PSA cutoff of 0.25 ng/ml, which may have affected classification of patients as those having residual disease, having BCR, or not being cured, which is another potential limitation. We believe that the data collected from telephone interviews are accurate and of good quality, since patients are naturally very worried about recurrence after prostatectomy and hope for it to be undetectable, and if it is not, they know and track their PSA values very well. In a previous LAPPRO publication, we reported an excellent agreement between patient and clinical reports after prostatectomy [18]. For example, the agreement (Kappa statistic) for receiving additional chemo- and/or radiotherapy after prostatectomy due to local recurrence or metastases was 0.78 at 12 mo. Furthermore, many events were reported to a higher degree by the patient reports compared with the CRFs, so if anything, we would likely overestimate the outcome of interest by asking the patients instead of physicians.

5. Conclusions

At 6 yr of follow-up in the prospective LAPPRO trial, we found an increase in recurrent and residual disease after RP from 13% to 22–23% compared with 2 yr of follow-up. RALP and RRP seem to have comparable oncological outcome 6 yr after surgery, although in a subgroup analysis stratified by D'Amico risk groups, we observed a significant benefit for RALP in high-risk patients. Longer follow-up time is needed to evaluate a possible survival benefit.

***Author contributions*:** Anders Bjartell had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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