



Platinum Priority – Prostate Cancer

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Biochemical Recurrence After Robot-assisted Radical Prostatectomy in a European Single-centre Cohort with a Minimum Follow-up Time of 5 Years

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Abstract

Background: Robot-assisted radical prostatectomy (RARP) is an increasingly commonly used surgical treatment option for prostate cancer (PCa); however, its longer-term oncologic results remain uncertain.

Objective: To report biochemical recurrence-free survival (BRFS) outcomes for men who underwent RARP ≥ 5 yr ago at a single European centre.

Design, setting, and participants: A total of 944 patients underwent RARP as monotherapy for PCa from January 2002 to December 2006 at Karolinska University Hospital, Stockholm, Sweden. Standard clinicopathologic variables were recorded and entered into a secure, ethics-approved database made up of those men with registered domiciles in Stockholm. The median follow-up time was 6.3 yr (interquartile range: 5.6–7.2).

Outcome measurements and statistical analysis: The outcome of this study was biochemical recurrence (BCR), defined as a confirmed prostate-specific antigen (PSA) of ≥ 0.2 ng/ml. Kaplan-Meier survival plots with log-rank tests, as well as Cox univariable and multivariable regression analyses, were used to determine BRFS estimates and determine predictors of PSA relapse, respectively.

Results and limitations: The BRFS for the entire cohort at median follow-up was 84.8% (95% confidence interval [CI], 82.2–87.1); estimates at 5, 7, and 9 yr were 87.1% (95% CI, 84.8–89.2), 84.5% (95% CI, 81.8–86.8), and 82.6% (95% CI, 79.0–85.6), respectively. Nine and 19 patients died of PCa and other causes, respectively, giving end-of-follow-up Kaplan-Meier survival estimates of 98.0% (95% CI, 95.5–99.1) and 94.1% (95% CI, 90.4–96.4), respectively. Preoperative PSA > 10 , postoperative Gleason sum $\geq 4 + 3$, pathologic T3 disease, positive surgical margin status, and lower surgeon volume were associated with increased risk of BCR on multivariable analysis. This study is limited by a lack of nodal status and tumour volume, which may have confounded our findings.

Conclusions: This case series from a single, high-volume, European centre demonstrates that RARP has satisfactory medium-term BRFS. Further follow-up is necessary to determine how this finding will translate into cancer-specific and overall survival outcomes.

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1. Introduction

Prostate cancer (PCa) is the most common nondermatologic cancer in Western men [1]. More than 90% of cases are organ-confined at diagnosis and are thus amenable to treatment by radical prostatectomy (RP), which has been shown to be superior to watchful waiting at 15-yr follow-up [2]. With the introduction of the robotic platform, the new millennium has seen an exponential rise in robot-assisted RP (RARP), which now accounts for many RPs done in developed countries [3]. However, there remains a lack of long-term oncologic data regarding this procedure, with one small RARP series of 184 patients that reports on biochemical recurrence (BCR) outcomes with a minimum follow-up of 5 yr [4]. The largest series in the literature reports prostate-specific antigen (PSA) relapse outcomes for 1384 patients with a median follow-up of 5.2 yr; it is from an American centre [5]. In this paper, we report BCR data on 904 patients treated at a single European centre who underwent RARP monotherapy from 2002 to 2006 and had a median follow-up of 6.3 yr.

2. Patients and methods

A total of 944 men with clinically localised or locally advanced (cT1–cT3) PCa underwent RARP by nine surgeons at Karolinska University Hospital, Stockholm, Sweden, from January 2002 to December 2006. Postoperative PSAs were taken at 6 wk, 6 mo, 12 mo, 18 mo, and 24 mo, and annually thereafter. The date of last follow-up updating for all patients was December 31, 2011. Forty of 944 of the men (4.2%) received adjuvant therapy (radiotherapy and/or hormones) and fulfilled the sole exclusion criterion; no patient received neoadjuvant therapy. Standard preoperative and postoperative clinicopathologic data on all subjects were prospectively entered into a secure, ethics-approved database. Information regarding pelvic lymphadenectomy was not available, as it was not routinely recorded when this study started in 2002, and thus we cannot be certain that our current indications for performing lymphadenectomy in intermediate- and high-risk disease were adhered to in all cases included in this study. RP specimens were subjected to whole-mount processing, sectioned according to the Stanford procedure, and evaluated by seven uropathologists. Postoperative PSA data for patients not presenting to our clinic but rather to other physicians' clinics were obtained from the records of laboratories in Stockholm, ensuring virtually complete data collection. BCR was defined as a confirmed PSA ≥ 0.2 ng/ml.

Clinicopathologic characteristics of a continuous nature were tested for normality using the Shapiro-Wilks test, and characteristics not normally distributed were reported as median and interquartile range (IQR). The study outcome was BCR, defined as a confirmed PSA ≥ 0.2 ng/ml. Kaplan-Meier survival analysis was used to visualise BCR-free survival (BRFS) outcomes, which were stratified by preoperative PSA, clinical risk group (low risk: preoperative PSA ≤ 10 and preoperative Gleason sum ≤ 6 ; intermediate risk: preoperative PSA 10–19.9 or preoperative Gleason sum 7; high risk: preoperative PSA ≥ 20 or preoperative Gleason sum ≥ 8 or cT3), postoperative Gleason sum, pathologic stage, surgical margin status, surgical margin status by pathologic stage, and surgeon volume (defined as the total number of RARP cases performed by an individual surgeon). Event-time distributions for the time to failure were compared using log-rank tests. Univariable and backward elimination (inclusion criterion: $p < 0.05$) multivariable Cox proportional hazard regression models incorporating age, prostate volume, surgeon volume, clinical stage, preoperative PSA, preoperative Gleason

sum, pathologic stage, postoperative Gleason sum, and surgical margin status were used to determine variables predictive of BCR, and hazard ratios (HRs) were computed for these risk factors. Patients with non-PCa deaths prior to BCR were censored at the time of death. All analyses were performed using SAS v.9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

Demographic and clinicopathologic summary statistics for the study cohort are reported in Table 1 and 2. The median age was 62.2 yr (IQR: 58.2–65.8), and the median preoperative PSA was 6.4 ng/ml (IQR: 4.8–9.0). The median prostate volume was 38.0 ml (IQR: 30.0–49.0), and the median surgeon volume was 131.8 (IQR: 51.3–245.5). A total of 60.2% of the study cohort was deemed low risk, 33.4% were intermediate risk, and 6.4% were high risk. The positive surgical margin rate was 21.6%; the overall BRFS was 84.8% (95% confidence interval [CI], 82.1–87.1) at a median follow-up time of 6.3 yr (IQR: 5.6–7.2) (Fig. 1A). The BRFS for all patients at 5, 7, and 9 yr was 87.1% (95% CI, 84.8–89.2), 84.5% (95% CI, 81.8–86.8), and 82.6% (95% CI, 79.0–85.6), respectively. The median time to BCR was 2.3 yr (IQR: 1.0–3.7). Nine and 19 patients died of PCa and other causes, respectively, with 16 of 19

Table 1 – Clinical characteristics

Clinical characteristics	Median	IQR
Patient age, yr	62.2	58.2–65.8
BMI, kg/m ²	25.6	24.0–27.3
Preoperative PSA, ng/ml	6.4	4.8–9.0
Prostate volume, ml	38.0	30.0–49.0
Surgeon volume	131.8	51.3–245.5
	<i>n</i>	%
Clinical T stage (missing <i>n</i> = 7)		
cT1	551	61.4
cT2	318	35.5
cT3	28	3.1
Preoperative PSA (missing <i>n</i> = 1)		
≤ 10	736	81.5
> 10	167	18.5
Clinical risk category (missing <i>n</i> = 3)		
Low	542	60.2
Intermediate	301	33.4
High	58	6.4
Surgeon volume (missing <i>n</i> = 2)		
1–50	222	24.6
51–100	142	15.7
101–150	132	14.6
> 150	406	45.0
Surgeries, no.		
2002	20	2.2
2003	70	7.7
2004	184	20.4
2005	266	29.4
2006	364	40.3
Nerve-sparing status (missing <i>n</i> = 16)		
Bilateral	340	38.3
Unilateral	310	34.9
None	238	26.8

IQR = interquartile range; BMI = body mass index; PSA = prostate-specific antigen.

Table 2 – Pathologic and follow-up characteristics

Pathologic characteristics	n	%
Preoperative Gleason sum (missing n = 4)		
≤6	664	73.8
3 + 4 = 7	168	18.7
4 + 3 = 7	44	4.9
≥8	24	2.7
Postoperative Gleason sum (missing n = 15)		
≤6	434	48.8
3 + 4 = 7	307	34.5
4 + 3 = 7	104	11.7
≥8	44	5.0
Pathologic T stage (missing n = 23)		
pT2	651	73.8
pT3a	192	21.8
pT3b	38	4.3
Surgical margin status (missing n = 6)		
Positive	194	21.6
Negative	704	78.4
Surgical margin status by pathologic stage (missing n = 23)		
Positive, pT2	104	16.0
Negative, pT2	547	84.0
Positive, pT3a	64	33.3
Negative, pT3a	128	66.7
Positive, pT3b	22	57.9
Negative, pT3b	16	42.1
Follow-up characteristics	Median	IQR
Overall follow-up time, yr	6.3	5.6–7.2
Time to biochemical recurrence, yr	2.3	1.0–3.7
Follow-up time in relapse-free and alive patients, yr	6.2	5.6–7.1
Time to death among deceased patients, yr	4.9	3.5–6.2
Biochemical recurrence	n	%
Present	135	15.2
Absent	753	84.8
Mortality	n	%
Prostate cancer-specific mortality	9	1.0
Other-cause mortality	19	2.1

IQR = interquartile range.

all-cause deaths occurring prior to PSA relapse, resulting in end-of-follow-up Kaplan-Meier survival estimates of 98.0% (95% CI, 95.5–99.1) and 94.1% (95% CI, 90.4–96.4) for PCa-specific and other-cause death, respectively. Kaplan-Meier plots and log-rank statistics showed significant differences in BCR outcome by surgeon volume, preoperative PSA, clinical risk group, pathologic Gleason sum, pathologic stage, surgical margin status, and surgical margin status stratified by pathologic stage (Fig. 1B–1H). Cox univariable analysis demonstrated age, surgeon volume, clinical stage, preoperative Gleason sum, preoperative PSA, postoperative Gleason sum, pathologic stage, and surgical margin status as predictors of BCR (Table 3). The variables that remained after backward elimination were surgeon volume (HR for 101–150 and >150: 1.601; 95% CI, 0.896–2.863; HR for 51–100 and >150: 2.036; 95% CI, 1.217–3.405; HR for 1–50 and >150: 2.062; 95% CI, 1.306–3.254), preoperative PSA (HR for >10 and ≤10:

Table 3 – Cox univariable analysis showing predictors of biochemical recurrence

Covariate	HR (95% CI)	p value
Age	1.037 (1.006–1.069)	0.0194
Prostate volume	0.995 (0.985–1.005)	0.3239
Surgeon volume		
>150*	1	–
101–150	1.311 (0.741–2.318)	0.3522
51–100	1.889 (1.153–3.092)	0.0115
1–50	2.457 (1.618–3.731)	<0.0001
Clinical T stage		
cT1*	1	–
cT2	1.598 (1.129–2.262)	0.0081
cT3	1.527 (0.616–3.786)	0.3613
Preoperative Gleason sum		
≤6*	1	–
3 + 4 = 7	2.443 (1.633–3.656)	<0.0001
4 + 3 = 7	5.336 (3.165–8.995)	<0.0001
≥8	7.204 (3.971–13.068)	<0.0001
Preoperative PSA		
≤10*	1	–
>10	2.425 (1.695–3.468)	<0.0001
Pathologic T stage		
pT2*	1	–
pT3a	2.680 (1.823–3.941)	<0.0001
pT3b	8.711 (5.386–14.091)	<0.0001
Postoperative Gleason sum		
≤6*	1	–
3 + 4 = 7	2.904 (1.821–4.633)	<0.0001
4 + 3 = 7	6.293 (3.777–10.485)	<0.0001
≥8	10.714 (6.098–18.824)	<0.0001
Surgical margin status		
Negative*	1	–
Positive	2.803 (1.985–3.959)	<0.0001

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen.
* Reference group.

Table 4 – Cox multivariable analysis showing predictors of biochemical recurrence selected according to backward elimination

Covariate	HR (95% CI)	p value
Surgeon volume		
>150*	1	–
101–150	1.601 (0.896–2.863)	0.1122
51–100	2.036 (1.217–3.405)	0.0068
1–50	2.062 (1.306–3.254)	0.0019
Preoperative PSA		
≤10*	1	–
>10	1.848 (1.259–2.713)	0.0017
Pathological T stage		
pT2*	1	–
pT3a	1.719 (1.131–2.614)	0.0113
pT3b	2.976 (1.610–5.500)	0.0005
Postoperative Gleason sum		
≤6*	1	–
3 + 4 = 7	2.160 (1.307–3.570)	0.0026
4 + 3 = 7	4.959 (2.853–8.620)	<0.0001
≥8	4.650 (2.298–9.408)	<0.0001
Surgical margin status		
Negative*	1	–
Positive	1.850 (1.249–2.740)	0.0021

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen.
* Reference group.

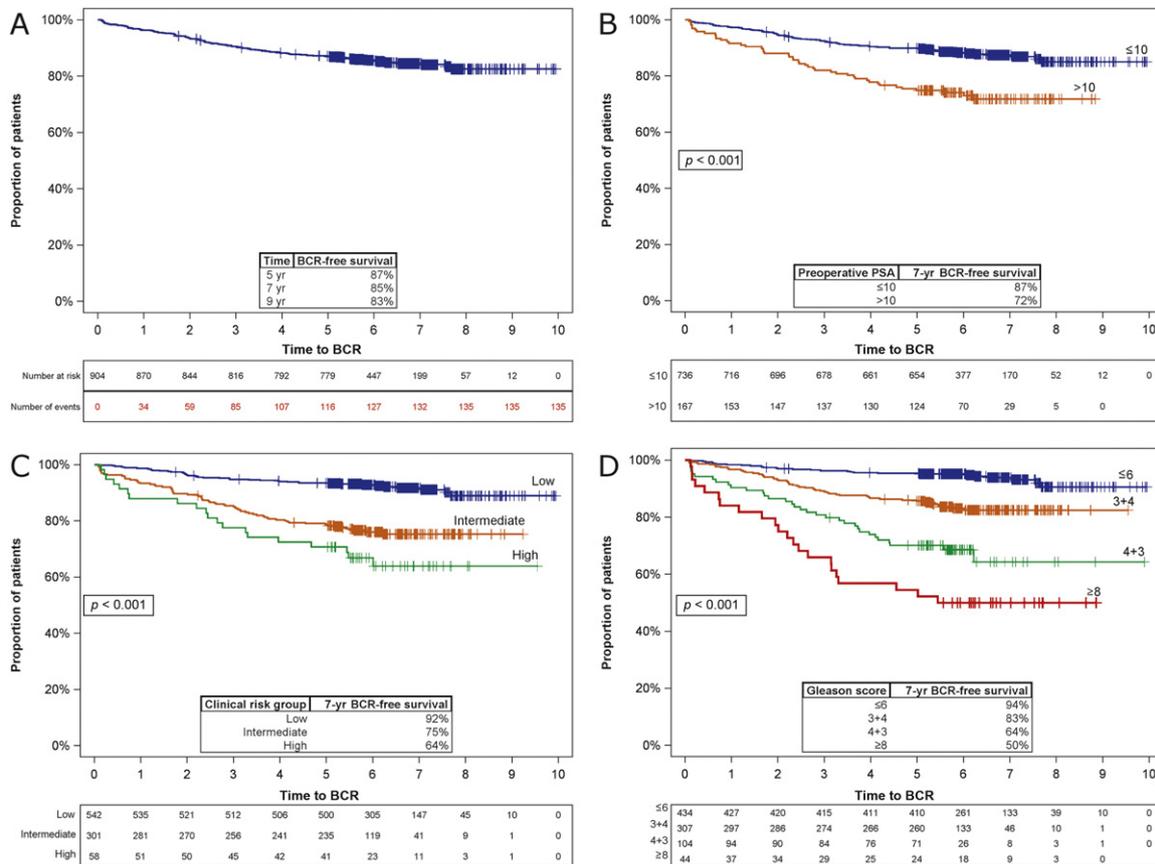


Fig. 1 – Kaplan-Meier survival curves for (A) all patients, (B) preoperative PSA, (C) clinical risk category, (D) postoperative Gleason sum, (E) pathologic stage, (F) surgical margin status, (G) surgical margin status by pathologic stage, and (H) surgeon volume. BCR = biochemical recurrence; PSA = prostate-specific antigen.

1.848; 95% CI, 1.259–2.713), postoperative Gleason sum (HR for 3 + 4 = 7 and ≤6: 2.160; 95% CI, 1.307–3.570; HR for 4 + 3 = 7 and ≤6: 4.959; 95% CI, 2.853–8.620; HR for ≥8 and ≤6: 4.650; 95% CI, 2.298–9.408), pathologic stage (HR for pT3a and pT2: 1.719; 95% CI, 1.131–2.614; HR for pT3b and pT2: 2.976; 95% CI, 1.610–5.500), and surgical margins (HR for positive and negative: 1.850; 95% CI, 1.249–2.740) (Table 4).

The excluded cohort of adjuvant radiotherapy patients had worse tumour characteristics than the study cohort with a higher percentage of preoperative PSA >10 (37.8%), intermediate- or high-risk disease (64.8%), pT3 (54.1%), postoperative Gleason sum ≥7 (73.0%), and positive surgical margins (73.0%). Indications for adjuvant radiotherapy in this group were left to the discretion of the treating clinician, and this excluded cohort demonstrated a high PSA relapse rate (40.5% at the end of follow-up).

4. Discussion

This case series from a single, high-volume, European centre of men treated by RARP ≥5 yr ago demonstrates an overall BRFS of 84.8% at a median follow-up of 6.3 yr (IQR: 5.6–7.2). Kaplan-Meier estimates of PCa-specific and other-cause mortality at a follow-up of 10 yr were 2.0% and 5.9%, respectively, but follow-up is too short to make conclusions based on these figures. Predictors of PSA relapse (in order of

importance based on the relative magnitude of the multivariable HRs) were postoperative Gleason sum ≥4 + 3, pT3 (especially pT3b) stage, surgeon volume, positive surgical margins, and preoperative PSA >10.

Dorin et al. recently reported on 2487 patients who underwent open RP and found a 10-yr PSA relapse rate of 8%, 17%, and 24% in D’Amico low-, intermediate-, and high-risk patients at a median follow-up of 7.2 yr [6]. This cohort had similar pT3 rates to our series (28.2% compared with 26.2%) and similar positive surgical margin rates to our series (26.0% compared with 21.8%), and our BCR outcomes appear comparable, with 8%, 15%, and 36% in the low-, intermediate-, and high-risk groups, respectively. Contemporary RARP series, in contrast, generally comprise more favourable patient populations, with lower percentages of pathologic Gleason sums and T3 stages [7,8]. A multi-institutional study of seven centres with 6169 RARP patients found a positive surgical margin rate of 15.7% [9], while a recent meta-analysis of 62 389 RARP patients found a rate of 16.2% [10], both findings lower than in our study cohort. This result is likely because PSA screening in our Swedish cohort from 2002 to 2006 was relatively uncommon compared with the predominantly American cohorts represented in the majority of the published literature.

Most RARP studies report only short-term follow-up outcomes, though Suardi et al. [4] recently reported BRFS

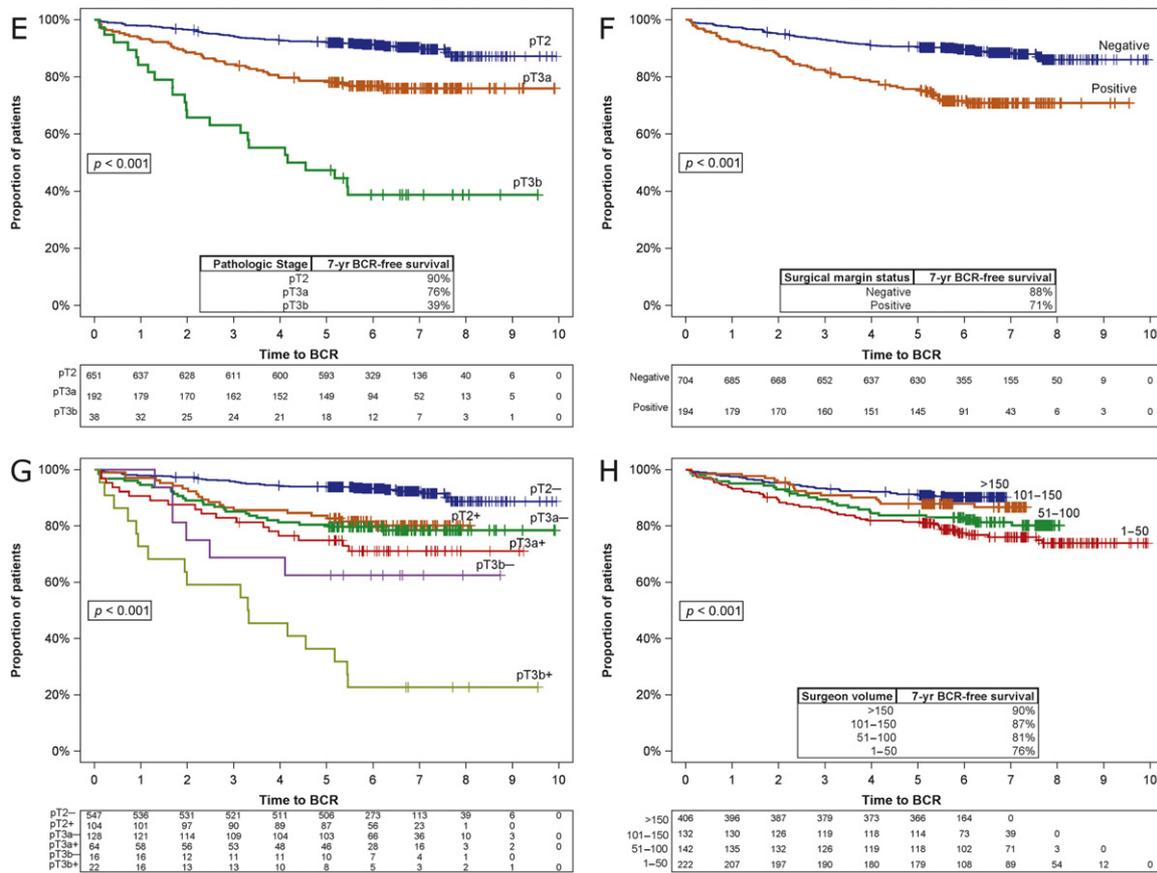


Fig. 1 (Continued).

after RARP for 184 patients with a follow-up of ≥ 5 yr and found an overall rate at 7 yr of 81.0%. The largest report of PSA outcomes in the RARP literature is from Menon et al. [5], who reported an overall BRFS of 86.4% for 1384 patients with a median follow-up of 60.2 mo (IQR: 37.2–69.7) and an identical 7-yr rate to that of Suardi et al. (and similar to our rate, 84.5%). The median time to BCR in the Menon study was 20.4 mo, which is shorter than the median time to BCR in our study, 27.7 mo, most likely because of their shorter follow-up time.

Among comparative studies reporting BCR in different surgical cohorts, Schroeck et al. [11] and Krambeck et al. [12] reported similar rates for RARP and open RP groups but at short follow-ups of 1 and 3 yr, respectively. A larger study by Barocas et al. [13] of 1904 patients from a concurrent series at Vanderbilt University demonstrated similar 3-yr BCR rates between these two modalities, but again the study was limited by a median follow-up of < 1 yr. A systematic review in 2007 [14] concluded that oncologic results after RARP were too immature at that time to allow comparisons with open and laparoscopic RP, and the situation had not changed with the follow-up review 2 yr later [15]. Recently, though, Drouin et al. [16] compared open RP, laparoscopic RP, and RARP PSA relapse rates for 239 patients with a mean follow-up of > 4 yr and showed equivalent actuarial 5-yr rates between modalities (12.2%, 11.9%, and 10.4%, respectively). A recent study

used propensity-score matching to balance age, race, preoperative PSA, biopsy Gleason score, and clinical stage between patients who underwent RARP, open RP, and laparoscopic RP at a single institution ($n = 522$ for each approach) [17]. The authors found no significant differences in BCR rates, but short mean follow-up in all modalities (1.3 yr for RARP, 1.4 yr for laparoscopic RP, and 2.5 yr for open RP). No robotic series, except that of Suardi et al. [4], has reported on RARP oncologic outcomes with ≥ 5 yr follow-up, and our series reported in this paper represents a larger sample size with the same minimum follow-up.

In our study, we found that preoperative PSA, pathologic Gleason sum, pathologic stage, and surgical margin status were predictors of PSA relapse after RARP. These factors have been consistently demonstrated as predictors of BCR in open series, and the Vanderbilt investigators showed the same predictors in their large cohort; additionally, they demonstrated that surgical approach did not predict recurrence [13]. Our data presented in this paper demonstrate that BCR rates worsen as pathologic stage increases and that within any single pathologic stage category, positive margins increase relapse rates. For patients with organ-confined disease, positive surgical margins result in BCR rates similar to those in patients with extracapsular extension and negative margins. This finding is in keeping with other studies [18,19] and suggests that the majority of men with

organ-confined disease will not experience a BCR despite having a positive surgical margin.

An interesting finding in this study was that surgeon volume was a predictor of BCR on multivariable analysis, with higher HRs as surgeon volume decreased. Klein et al. [20] studied 7683 patients who underwent open RP performed by 72 different surgeons and demonstrated that the highest-volume surgeons had the lowest recurrence rates when other variables were adjusted for. The absolute risk difference in 5-yr PSA relapse rates in a patient receiving treatment from a surgeon with 10 compared with 250 prior open RPs was 6.6% (95% CI, 3.4–10.3), 12.0% (95% CI, 6.9–18.2), and 9.7% (95% CI, 1.2–18.2) for low-, intermediate-, and high-risk patients, respectively. A study by Sooriakumaran et al. [21] demonstrated that surgical margin rates continue to fall in RARP surgeons even after >1500 cases; this finding, together with our finding that BCR is doubled in cases in which the surgeon has done <100 prior procedures compared with cases in which the surgeon has performed >150 operations, demonstrates that the influence of surgeon volume on oncologic outcome is present in robotic series as well. It is also known that higher-volume RARP surgeons decrease the cost of the procedure, further supporting the argument that RARP should be performed only by such surgeons [22].

The major strength of our study is that it represents the largest reported RARP series with a minimum follow-up time of 5 yr, and the study includes all patients living in a specified demographic region, regardless of whether they came to our clinic for follow-up. No patient received neoadjuvant treatment, and only 40 of 944 patients (4.2%) received adjuvant treatment and were thus excluded. These 40 cases generally harboured more aggressive pathologic tumour characteristics than the average study participant; however, given the small numbers involved, the impact on the results would be minimal.

Our study is not without limitations. Nodal status was not recorded in this study, since our database does not capture this variable. Many patients did not undergo pelvic lymphadenectomy, since the rationale for this procedure was uncertain when our series started in 2002. Also, no measure of tumour volume (according to preoperative or postoperative pathology) was recorded in our series. Both these parameters are well-established predictors of BCR after RP and thus might have confounded our multivariable results [23–25]. It is also important to remember that BCR does not necessarily lead to clinical recurrence or cancer-specific mortality, and clinical progression-free BCR might reflect the recurrence of indolent PCa or the presence of benign prostatic tissue left behind after surgery [26]. Hence, it is necessary to follow up our cohort further and determine the impact of BCR on longer-term oncologic end points.

5. Conclusions

We have reported the largest RARP series to date with follow-up on all patients of ≥ 5 yr and ≤ 10 yr. The rate of

BRFS is 84.8% at a median follow-up of 6.3 yr, and further follow-up is required to determine how this outcome will translate to cancer-specific and all-cause mortality before definitive conclusions regarding the oncologic safety of RARP can be confirmed.

Author contributions: Peter Wiklund 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.

Study concept and design: Sooriakumaran, Wiklund, Haendler, Steineck. **Acquisition of data:** Haendler, Nyberg, Nilsson, Carlsson, Hosseini, Adding, Jonsson, Ploumidis, Egevad.

Analysis and interpretation of data: Nyberg, Sooriakumaran, Steineck, Wiklund.

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Critical revision of the manuscript for important intellectual content: Wiklund, Steineck.

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