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Platinum Priority – Prostate Cancer

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Biochemical Recurrence Following Robot-Assisted Radical Prostatectomy: Analysis of 1384 Patients with a Median 5-year Follow-up

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Abstract

Background: There is a paucity of data on long-term oncologic outcomes for patients undergoing robot-assisted radical prostatectomy (RARP) for prostate cancer (PCa).

Objective: To evaluate oncologic outcomes in patients undergoing RARP at a high-volume tertiary center, with a focus on 5-yr biochemical recurrence-free survival (BCRFS).

Design, setting, and participants: The study cohort consisted of 1384 consecutive patients with localized PCa who underwent RARP between September 2001 and May 2005 and had a median follow-up of 60.2 mo. No patient had secondary therapy until documented biochemical recurrence (BCR). BCR was defined as a serum prostate-specific antigen ≥ 0.2 ng/ml with a confirmatory value. BCRFS was estimated using the Kaplan-Meier method. Event-time distributions for the time to failure were compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression models were used to determine variables predictive of BCR.

Intervention: All patients underwent RARP.

Measurements: BCRFS rates were measured.

Results and limitations: This cohort of patients had moderately aggressive PCa: 49.0% were D'Amico intermediate or high risk on biopsy; however, 60.9% had Gleason 7–10 disease, and 25.5% had $\geq T3$ disease on final pathology. There were 189 incidences of BCR (31 per 1,000 person years of follow-up) at a median follow-up of 60.2 mo (interquartile range [IQR]: 37.2–69.7). The actuarial BCRFS was 95.1%, 90.6%, 86.6%, and 81.0% at 1, 3, 5, and 7 yr, respectively. In the patients who recurred, median time to BCR was 20.4 mo; 65% of BCR incidences occurred within 3 yr and 86.2% within 5 yr. On multivariable analysis, the strongest predictors of BCR were pathologic Gleason grade 8–10 (hazard ratio [HR]: 5.37; 95% confidence interval [CI], 2.99–9.65; $p < 0.0001$) and pathologic stage T3b/T4 (HR: 2.71; 95% CI, 1.67–4.40; $p < 0.0001$).

Conclusions: In a contemporary cohort of patients with localized PCa, RARP confers effective 5-yr biochemical control.

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1. Introduction

Radical prostatectomy (RP) is an effective form of treatment for localized prostate cancer (PCa) [1]. Earlier studies indicate that an estimated 35% of men will experience a biochemical recurrence (BCR) within 10 yr of undergoing RP [2–4]. With the introduction of prostate-specific antigen (PSA) screening, however, there has been a gradual stage and risk migration in PCa, and more men are now diagnosed at an earlier age, with a lower PSA and localized disease [5–7]. Thus, BCR rates from earlier studies may not reflect BCR rates in contemporary patients. Few studies have concentrated on BCR in patients diagnosed after 2000.

In the United States, robot-assisted radical prostatectomy (RARP) has become the surgical treatment of choice for many men with localized PCa. A systematic review of the RARP literature stressed the paucity of BCR data in patients undergoing RARP [8]. Robotic surgery is relatively new, the first robotic urologic program having started at our institution in 2000 [9,10]. The initial patients in this cohort are approaching 10 yr of follow-up. The purpose of this study was to examine oncologic outcomes in patients undergoing RARP between 2001 and 2005.

2. Material and methods

2.1. Patient selection and treatment

From 2000 to 2010, >5000 patients with localized PCa have undergone RARP at our institution using the techniques described by Menon et al [10–12]. Our database comprised 1581 patients who underwent RARP between September 2001 and May 2005 and were eligible for a minimum follow-up of 5 yr. Following exclusion of patients who did not have recorded PSA values postoperatively ($n = 126$), received prior hormone therapy or radiation therapy ($n = 48$), had incomplete biopsy data ($n = 14$), or had adjuvant treatments before documented BCR ($n = 9$), the remaining 1384 patients were the subjects of the present analysis.

All patients had a minimum of six core prostate biopsies, and all biopsies were reviewed by a referee pathologist. The preoperative variables recorded included age, PSA level, biopsy Gleason score, biopsy tumor volume, clinical stage (American Joint Committee on Cancer 2009 guidelines), and body mass index (BMI).

RARP was performed by either MM (1182 patients) or JOP (399 patients). All patients underwent video analysis of the procedure for the first 3 yr of the study, enabling standardization of technique. Nerve sparing was performed in patients who were potent (Sexual Health Inventory for Men >17), the technique evolving during the course of the study [13]. Pelvic lymph node dissection (PLND) was performed only if the probability of lymph node metastasis was >1%, as determined by genetic adaptive neural network analysis [14]. Patients with low- to intermediate-risk disease had PLND limited to the external iliac and obturator zones, whereas extended PLND was performed for patients with palpable T2b–T3 disease, Gleason score of 8–10, or PSA >10 ng/ml.

2.2. Pathologic assessment

The RP specimens were examined according to the Stanford protocol [15]. Pathologic variables evaluated included pathologic stage, Gleason score, tumor volume, prostate weight, lymph node status, perineural invasion, angiolymphatic invasion, and surgical margin status. *Extra-prostatic extension* (EPE) was defined as spread of cancer into soft tissue

or skeletal muscle; *positive surgical margin* was defined as extension of cancer to the inked surface. Node packets were sent separately. All visible and palpable lymph nodes were dissected and submitted for microscopic examination to evaluate for the presence of metastasis.

2.3. Follow-up

Demographic and follow-up data were collected from a prospective prostatectomy electronic database, institutional electronic medical records, hospital billing records, outpatient medical records, and communication with patients and referring physicians. All patients were queried electronically at 3-mo intervals for the first 12 mo, semiannually during the second year, and annually thereafter. For patients without PSA records within the last 12 mo, follow-up e-mails were sent in April and June 2010. Database management was performed by individuals who were not involved in direct clinical care. The study protocol was approved by the institutional review board of Henry Ford Hospital. Data collection and follow-up correspondence were conducted in accordance with the US Health Insurance Portability and Accountability Act. BCR was defined following the guidelines of the American Urological Association Localized Prostate Cancer Update Panel report [16].

2.4. Statistical analysis

The probability of BCR-free survival (BCRFS) was estimated using the Kaplan-Meier method, and survival curves among groups were compared using the log-rank test. The impact of clinical and pathologic features on BCRFS was analyzed using univariable and multivariable Cox proportional hazard regression models; the proportionality assumption was tested and found to hold (for details, see Appendix). Three models were created in a nonstepwise fashion. The first two models considered preoperative predictors only, including patient age (coded as ≥ 60 and <60 yr of age), BMI (coded as <25, 25–30, ≥ 30), perineural invasion (on biopsy), and procedure year; the first incorporated preoperative PSA (coded as <10, 10.1–20, and >20 ng/ml), biopsy Gleason score, and clinical stage; and the second D'Amico risk group. The third model considered predictors of BCR available postoperatively: tumor volume (coded as <15% or $\geq 15\%$), pathology Gleason score, pathologic stage (coded as T2, EPE, seminal vesical invasion [SVI]/T4), perineural and angiolymphatic invasion (as determined on final specimen), margin status, and nerve-sparing approach together with age and PSA. All statistical analyses were performed by a qualified biostatistician (MD) using SAS v.9.1 (SAS Institute, Cary, NC, USA). All p values are two-sided and considered statistically significant if <0.05.

3. Results

3.1. Preoperative and pathologic characteristics

Clinical and pathologic variables for the study cohort (1384 patients) are depicted in Table 1. The mean age was 60.0 yr (standard deviation [SD]: ± 7.1), and median serum PSA was 5.2 ng/ml (interquartile range [IQR]: 4.2–7.1). Mean BMI was 27.5 (SD: ± 3.6), prostate weight (on final specimen) was 48.3 g (SD: ± 20.1), and percent tumor volume was 17.5% (SD: ± 13.4).

3.2. Follow-up and cancer control

The median follow-up was 5.0 yr (IQR: 3.1–5.8 yr). There were 189 incidences of BCR, 13 patients developed

Table 1 – Clinical and pathologic features of cohort (n = 1384)

Characteristics		
Continuous		Mean (SD)
Patient age, yr		60.0 (±7.1)
BMI		27.5 (±3.6)
Prostate weight, g		48.3 (±20.1)
Percent tumor volume, %		17.5 (±13.4)
		Median (IQR)
Preoperative PSA, ng/ml		5.2 (4.2–7.1)
Follow-up, mo		60.2 (37.2–69.7)
Category	n	%
Clinical stage:		
T1a–c	1017	73.5
T2a	208	15.0
T2b	56	4.0
T2c	71	5.1
T3a	27	2.0
T3b	5	0.4
Biopsy Gleason score:		
5 or 6	844	61.0
3 + 4	347	25.1
4 + 3	103	7.5
8–10	89	6.4
Missing	1	–
Perineural invasion (biopsy):		
Absent	1236	89.4
Present	146	10.6
Missing	2	–
Nerve sparing [†] :		
Partial	716	51.7
Prostatic fascia sparing ^{**}	597	43.2
Wide excision	71	5.1
Pathologic Gleason score:		
6	541	39.1
3 + 4	563	40.7
4 + 3	165	11.9
8–10	115	8.3
Pathologic stage:		
T2a	196	14.1
T2b	23	1.7
T2c	813	58.7
T3a	293	21.2
T3b–T4	59	4.3
Margins [†] :		
Negative	1036	74.9
Positive	348	25.1
Perineural invasion ^{††}		
Absent	552	39.9
Present	832	60.1
Angiolymphatic invasion ^{††} :		
Absent	1347	97.3
Present	37	2.7
Procedure year		
2001	47	3.4
2002	254	18.4
2003	303	21.9
2004	528	38.2
2005	252	18.2

SD = standard deviation; BMI = body mass index; IQR = interquartile range.

[†] Partial nerve sparing: preservation of the dominant neurovascular distribution on the posterolateral prostate. Prostatic fascia sparing: alternatively described as *veil of Aphrodite*, *intrafascial*, and *high anterior release*.

^{**} Unilateral or bilateral.

[†] Organ confined: 135 of 1032 (13.1%); non-organ confined: 213 of 352 (60.5%).

^{††} On final pathology.

metastatic disease, 7 patients died of PCa, and 29 patients died of competing causes. All but one patient, with a small-cell carcinoma of the prostate, had a rise in PSA preceding metastasis or death. The BCR was 31 per 1,000 person years of follow-up; metastatic rates and cancer-specific death rates were 2 patients and 1 patient per 1000 person years of follow-up, respectively.

Because only 16 patients were followed at 8 yr, much of the analysis is restricted to 7 yr of follow-up (Fig. 1). The actuarial BCRFS rate was 90.7% (95% confidence interval [CI], 89.0–92.1) at 3 yr, 86.6% (95% CI, 84.6–88.4) at 5 yr, and 81.0% (95% CI, 77.6–84.0) at 7 yr. The median time to BCR was 20.4 mo; 65% of occurrences ($n = 123$) happened within 3 yr and 86.2% ($n = 163$) by 5 yr.

Fig. 2 demonstrates the actuarial BCRFS rate following RARP, stratified by D'Amico risk group. The BCRFS was 96.8%, 95.1%, and 92.6% in low-risk patients; 86.7%, 80.2%, and 69.8% in intermediate-risk patients; and 78.2%, 72.0%, and 67.5% in high-risk patients at 3, 5, and 7 yr following RARP, respectively (pooled p value <0.0001). The pairwise p value was <0.0001 between low- and medium-risk groups and 0.0335 between medium- and high-risk groups.

Fig. 3 shows BCRFS stratified by Gleason score in patients with organ-confined (Fig. 3a) or non-organ-confined (Fig. 3b) disease. Pooled p values were <0.0001 among all Gleason grades in both organ-confined and non-organ-confined disease. Pairwise comparisons in organ-confined disease were 3 + 3 versus 3 + 4 ($p < 0.0001$), 3 + 4 versus 4 + 3 ($p = 0.5729$), 3 + 4 versus 8–10 ($p = 0.0068$), and 4 + 3 versus 8–10 ($p = 0.0657$). Pairwise comparisons in non-organ-confined disease were 3 + 3 versus 3 + 4 ($p = 0.3981$), 3 + 4 versus 4 + 3 ($p = 0.0002$), 3 + 4 versus 8–10 ($p < 0.0001$), and 4 + 3 versus 8–10 ($p = 0.0017$). Table 2 and Table 3 summarize data of the univariable and multivariable analyses for predictors of BCR. Among preoperative variables (Table 2), PSA ≥ 20 ng/ml (hazard ratio [HR]: 6.16; 95% CI, 3.45–11.01; $p < 0.0001$) and Biopsy Gleason 4 + 3 (HR: 6.17; 95% CI, 3.96–9.62; $p < 0.0001$) were the strongest predictors of BCR. When considering pathologic variables available postoperatively (Table 3), pathologic Gleason grade was the strongest predictor of BCR, with an HR of 1.90 (95% CI, 1.13–3.19; $p = 0.0158$) for Gleason 3 + 4, 3.05 (95% CI, 1.71–5.46; $p = 0.0002$) for Gleason 4 + 3, and 5.37 (95% CI, 2.99–9.65; $p < 0.0001$) for Gleason 8–10 when compared to Gleason 6.

4. Discussion

RARP has become the most widely used form of surgical treatment of localized PCa in the United States, yet there is a paucity of intermediate- and long-term oncologic follow-up data [8]. Badani et al reported a BCR rate of 7.3% in 2766 consecutive patients undergoing RARP at our institution; however, the median follow-up was only 22 mo [17]. In a paper that focused on surgical technique, Murphy et al reported on 400 patients who underwent RARP between 2003 and 2006, with a median follow up of 22 mo [18]. Barocas et al reported 3-yr BCRFS rates of 93.1% and 55.4%

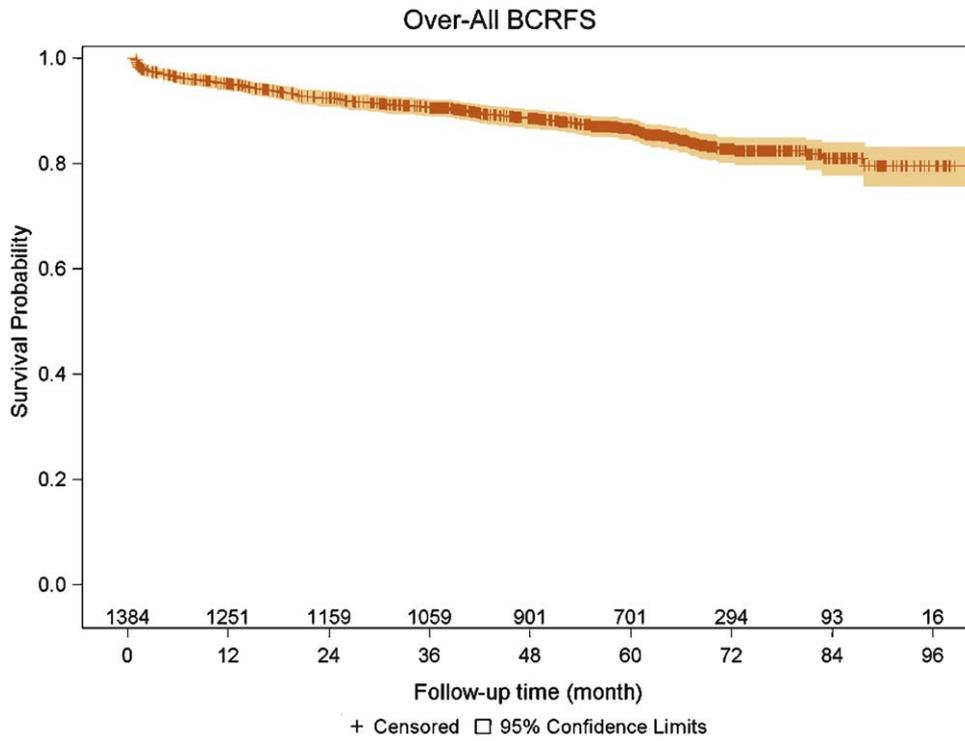


Fig. 1 – Kaplan-Meier-estimated probability of biochemical recurrence-free survival. The number at risk is given above the x-axis. The 95% confidence interval is represented by the shaded area. BCRFS = biochemical recurrence-free survival.

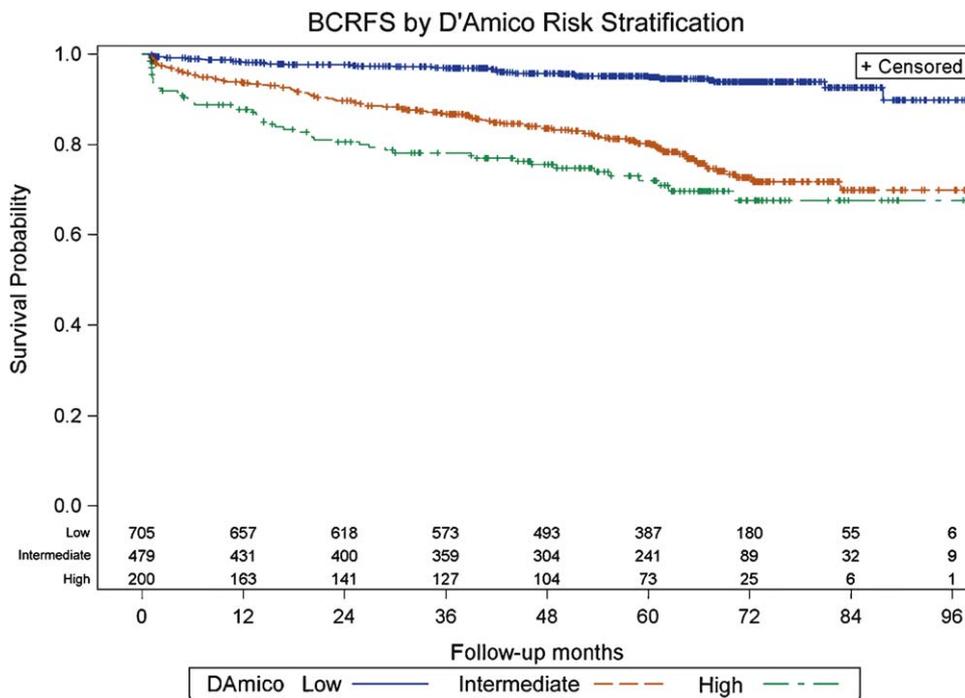


Fig. 2 – Biochemical recurrence-free survival by preoperative D'Amico risk groups. The number at risk per D'Amico risk group is given above the x-axis. The pooled p value ascertained by the log-rank test is <0.0001 for all curves. BCRFS = biochemical recurrence-free survival.

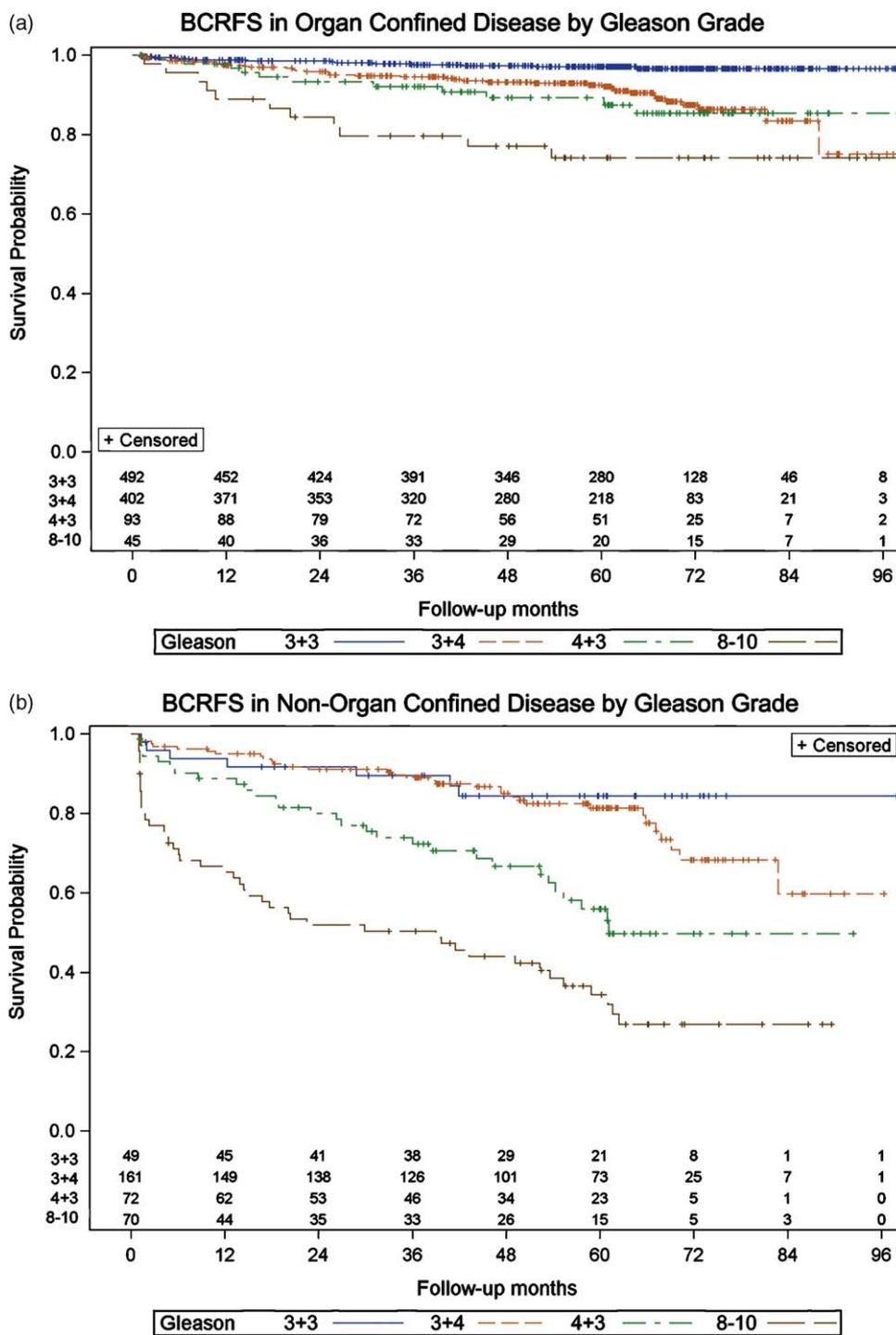


Fig. 3 – Biochemical recurrence-free survival stratified by Gleason grade for (a) organ-confined disease and (b) non-organ-confined disease. The number at risk per Gleason grade is given above the x-axis. The pooled *p* value ascertained by the log-rank test is <0.0001 for all curves. BCRFS = biochemical recurrence-free survival.

for pT2 and pT3 disease, respectively, but with a median follow-up of 8 mo [19].

The current study evaluated 1384 men undergoing RARP at our institution. Some of these patients were included in the cohort reported by Badani et al; however, this analysis is restricted to patients operated on from 2001 to 2005 and thus eligible for a follow-up of 5–8 yr. In this group, the

probability of BCR was 9.3% (95% CI, 7.9–11.0) at 3 y, 13.4% (95% CI, 11.6–15.4) at 5 yr, and 17.6% (95% CI, 15.2–20.3) at 7 yr. This finding is consistent with BCR rates reported in large open series [2–4,20].

Although this report addresses BCR in patients undergoing RARP, it is not meant to imply that these rates are a function of surgical approach. For example, in a paper

Table 2 – Univariable and multivariable Cox proportional hazards regression models of biochemical recurrence incorporating preoperative and biopsy information

Covariate	Univariable analysis		Multivariable analysis			
	HR (95% CI)	p value	Model 1*		Model 2†	
			HR (95% CI)	p value	HR (95% CI)	p value
Age, yr:						
<60**	1	–	1	–	1	–
≥60	1.39 (1.04–1.87)	0.0007	0.98 (0.72–1.32)	0.8792	1.20 (0.89–1.61)	0.2358
BMI:						
<25 kg/m ² **	1	–	1	–	1	–
25–30 kg/m ²	1.28 (0.83–1.96)	0.2654	1.07 (0.72–1.60)	0.7257	1.15 (0.78–1.71)	0.4846
≥30 kg/m ²	1.14 (0.77–1.69)	0.5075	1.14 (0.74–1.76)	0.5600	1.21 (0.78–1.86)	0.3910
Preoperative PSA:						
≤10 ng/ml**	1	–	1	–	–	–
10.1–20.0 ng/ml	2.98 (2.03–4.38)	<0.0001	2.61 (1.76–3.86)	<0.0001	–	–
>20 ng/ml	9.17 (5.28–15.93)	<0.0001	6.16 (3.45–11.01)	<0.0001	–	–
Biopsy Gleason grade:						
5 or 6**	1	–	1	–	–	–
3 + 4	3.39 (2.36–4.87)	<0.0001	3.05 (2.11–4.43)	<0.0001	–	–
4 + 3	6.99 (4.55–10.73)	<0.0001	6.17 (3.96–9.62)	<0.0001	–	–
8–10	6.22 (3.95–9.80)	<0.0001	4.84 (3.00–7.80)	<0.0001	–	–
Clinical stage:						
T1c/T2a**	1	–	1	–	–	–
≥T2b	1.65 (1.12–2.45)	0.0118	1.42 (0.94–2.16)	0.1004	–	–
D'Amico risk group*:						
Low**	1	–	–	–	1	–
Intermediate	4.28 (2.92–6.28)	<0.0001	–	–	4.07 (2.77–5.98)	<0.0001
High	6.16 (4.02–9.45)	<0.0001	–	–	5.65 (3.62–8.83)	<0.0001
Perineural invasion†:						
Negative**	1	–	1	–	1	–
Positive	2.30 (1.60–3.32)	<0.0001	1.39 (0.94–2.07)	0.1016	1.59 (1.09–2.32)	0.0168
Procedure year††:						
2001**	1	–	1	–	1	–
>2001	0.93 (0.82–1.07)	0.3195	0.88 (0.77–1.00)	0.0569	0.88 (0.77–1.00)	0.0546

HR = hazard ratio; CI = confidence interval; BMI = body mass index; PSA = prostate-specific antigen.
* Multivariable model 2 was generated using the D'Amico risk group as a predictor, supplanting grade, stage, and PSA.
** Reference group.
† On biopsy.
†† Incorporated as a continuous value.

reflecting trifecta outcomes, Eastham et al reported BCR rates in 1577 patients treated with open RP from 2000 to 2006. In a cohort possessing clinical and pathologic features similar to ours, they found a BCR rate of 9% at a median follow-up of 2 yr. Similarly, Guillonnet et al found a 3-yr progression-free survival of 90.5% in 1000 patients who underwent laparoscopic RP (LRP) between 1998 and 2002, with median follow-up of 12 mo [21]. Pavlovich et al published a series of 508 men who underwent LRP between 2001 and 2005 [22]. BCRFS was calculated at 94% but with a mean follow-up of 13 mo. Lein et al, in a study of 1000 LRP cases from 1999 to 2004, demonstrated 5-yr actuarial BCRFS of 90% for pT2 and 65% for pT3 cancer at a median follow-up of 28.8 mo [23]. Granted, the median follow-up in these series is substantially shorter, but the results are in concordance with our report despite the difference in surgical approach. Thus, it is our view that the biology of the tumor trumps surgical approach in determining oncologic outcomes in patients with PCa. Nevertheless, our study

shows that oncologic outcomes were not compromised by robotic surgery at a high-volume center. The pathologic features predictive of treatment failure do not appear to have changed appreciably in the past 20 yr. Gleason score, PSA, pathologic stage, and margin status still appear to predict BCR in a multivariable analysis, with extracapsular disease, pathologic Gleason grade, and PSA having the greatest impact.

There are several strengths to our study. First, to our knowledge, this study provides the longest follow-up of patients with localized PCa treated surgically in the current decade, whether open, laparoscopic, or robotic. Second, it provides the longest follow-up of the largest number of patients treated with RARP. Follow-up was excellent, with only 7.9% of patients (126 of 1581) not reporting postoperative PSA values. Finally, no patient in this cohort received secondary treatment until documented BCR, so this study gives an excellent portrayal of the natural history of localized PCa treated with surgery as the single modality.

Table 3 – Univariable and multivariable Cox proportional hazards regression models of biochemical recurrence incorporating variables from final pathology

Covariate	Univariable analysis		Multivariable analysis	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age, yr:				
<60*	1	–	1	–
≥60	1.44 (1.07–1.92)	0.0148	1.15 (0.85–1.55)	0.3675
Preoperative PSA:				
≤10.0 ng/ml†	1	–	1	–
10.1–20.0 ng/ml	2.98 (2.03–4.38)	<0.0001	1.64 (1.10–2.45)	0.0156
>20 ng/ml	9.17 (5.28–15.93)	<0.0001	1.95 (1.06–3.58)	0.0318
Tumor volume:				
<15%‡	1	–	1	–
≥15%	3.07 (2.16–4.35)	<0.0001	1.13 (0.77–1.66)	0.5356
Pathology Gleason grade:				
6*	1	–	1	–
3 + 4	3.35 (2.06–5.46)	<0.0001	1.90 (1.13–3.19)	0.0158
4 + 3	7.01 (4.13–11.88)	<0.0001	3.05 (1.71–5.46)	0.0002
8–10	16.90 (10.24–27.88)	<0.0001	5.37 (2.99–9.65)	<0.0001
Stage:				
T2*	1	–	1	–
EPE	4.60 (3.36–6.30)	<0.0001	1.78 (1.21–2.62)	0.0036
SVI/T4	11.18 (7.38–16.94)	<0.0001	2.71 (1.67–4.40)	<0.0001
Margins:				
Negative*	1	–	1	–
Positive	4.87 (3.65–6.51)	<0.0001	2.43 (1.72–3.42)	<0.0001
Perineural invasion**:				
Negative*	1	–	1	–
Positive	2.97 (2.07–4.26)	<0.0001	1.33 (0.89–1.99)	0.1584
Angiolymphatic invasion*:				
Negative†	1	–	1	–
Positive	5.54 (3.44–8.91)	<0.0001	2.15 (1.30–3.57)	0.0030
Nerve sparing†:				
Partial*	1	–	–	–
Prostatic fascia sparing††:	0.46 (0.32–0.64)	<0.0001	0.70 (0.48–1.02)	0.0633
Wide excision	1.64 (1.01–2.67)	0.0437	1.01 (0.62–1.65)	0.9653
Procedure year‡:				
2001*	1	–	1	–
>2001	0.93 (0.82–1.07)	0.3173	0.94 (0.82–1.08)	0.4035

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen; EPE = extraprostatic extension; SVI = seminal vesical invasion.

* Reference group.

** On final specimen.

† Partial nerve sparing: preservation of the dominant neurovascular distribution on the posterolateral prostate; prostatic fascia sparing: alternatively described as *veil of Aphrodite*, *intrafascial*, and *high anterior release*.

†† Unilateral or bilateral.

‡ Incorporated as a continuous value.

There are several important disclaimers. Although this study was performed at a single institution by two experienced surgeons, it encompassed the learning curve for both surgeons and, indeed, for the development of the RARP technique. Klein et al have reported that surgeon experience, independent of surgical volume, affects BCR [24], suggesting that there are hitherto unquantifiable skills that go into surgical ability—at least as far as open RP goes. This hypothesis seems reasonable for RARP, as well. Thus, our results may not be generalizable. However, the Klein report also raises the intriguing possibility that we are overestimating BCR following RARP, because the study included our learning curve. A further limitation of the

study is patient selection. The surgeons in this study preferentially treated patients with D'Amico moderate- to high-risk disease—to wit, 49.1% of patients had a biopsy Gleason score ≥ 7 . BCR rates may be lower or higher in practices that treat patients with less or more aggressive cancer. Finally, the median follow-up in this study was 5 yr. Although this period is long enough to draw meaningful conclusions about BCR, it is too short to opine about metastasis- and cancer-specific survival. That said, the fact that deaths from PCa occurred in only 1 per 1,000 person years of follow-up should provide a strong endorsement of the curative role of RP for patients with localized PCa treated in the contemporary era.

5. Conclusions

This study reports BCR rates in a series of patients with localized PCa who underwent RARP between 2001 and 2005. It represents the longest follow-up with this surgical approach. In a cohort where the majority of patients possessed Gleason ≥ 7 disease and slightly more than one patient in four had non-organ-confined cancer, the actuarial BCR was 13.6% at 5 yr—the time of median follow-up. The strongest predictors of BCR were pathologic stage and pathologic Gleason grade. This report provides a framework for patients with localized PCa undergoing surgery to estimate oncologic outcomes.

Author contributions: Jesse Sammon 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: Diaz, Menon, Siddiqui.

Acquisition of data: Bhandari, Gupta, Lane, Menon, Peabody, Sammon, Siddiqui.

Analysis and interpretation of data: Diaz, Menon, Sammon.

Drafting of the manuscript: Menon, Rogers, Siddiqui, Sammon.

Critical revision of the manuscript for important intellectual content: Diaz, Menon, Rogers, Sammon.

Statistical analysis: Diaz, Sammon.

Obtaining funding: Menon.

Administrative, technical, or material support: Bhandari, Menon.

Supervision: Menon.

Other (specify): None.

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Appendix A

Type of nerve sparing

From 2001 to 2003, nerve sparing was done using the Lepor-Walsh technique, termed *conventional* in this paper [25]. From 2003 onward, the prostate fascia-sparing approach (also called *veil of Aphrodite*, *intrafascial*, *curtain dissection*, and *high anterior release*) was used where indicated [13,26,27]. We acknowledge the imprecision of such categorization.

Cox proportional hazards analysis

We had initially identified four PSA groups: 0–4, 4.1–10, 10.1–20, and >20. However, the hazards were not proportional for groups 0–4.0 and 4.1–10. Therefore, these were combined into a single group: PSA = 0–10. Similarly, separating clinical stage into T1 and T2a violated the proportional hazards requirements, so these two stages

were combined. As this combination resulted in a very large group, all other categories were combined into a single group. This categorization of variables satisfied the proportional hazards assumption.

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