Posterior Rhabdosphincter Reconstruction During Robotic Assisted Radical Prostatectomy: Results From a Phase II Randomized Clinical Trial

Douglas E. Sutherland, Brian Linder, Anna M. Guzman, Mark Hong, Harold A. Frazier, II, Jason D. Engel* and Fernando J. Bianco, Jr.†

From the Department of Urology, George Washington University, Washington, D. C.

Abbreviations and Acronyms

bPLND = bilateral pelvic lymph node dissection

EPIC = Expanded Prostate Cancer Index Composite

I-PSS = International Prostate Symptom Score

PRR = posterior rhabdosphincter reconstruction

RARP = robotic assisted radical prostatectomy

RCT = randomized clinical trial

Submitted for publication August 15, 2010.

Study received institutional review board approval.

Presented at annual meeting of American Urological Association, Chicago, Illinois, April 25–30, 2009.

* Financial interest and/or other relationship with Vivus and TIMM Medical.

† Correspondence: Columbia University Division of Urology, Mount Sinai Medical Center, 4302 Alton Rd., Suite 540, Miami Beach, Florida 33140 (telephone: 305-515-9887; FAX: 305-749-8159; e-mail: research@drbianco.org).

See Editorial on page 1186.

For another article on a related topic see page 1519.

Purpose: Posterior rhabdosphincter reconstruction following radical prostatectomy was designed to improve early urinary continence. We executed a randomized clinical trial to test this conjecture in men undergoing robotic radical prostatectomy.

Materials and Methods: We conducted a phase II randomized clinical trial intended to detect a 25% difference in 3-month continence outcomes defined by a patient response of 0 or 1 to question 5 of the Expanded Prostate Cancer Index Composite questionnaire urinary domain, comparing standard running vesicourethral anastomosis (controls) to posterior rhabdosphincter reconstruction followed by standard running vesicourethral anastomosis (posterior rhabdosphincter reconstruction treated). Patients had clinically localized prostate cancer and were blinded. Surgeons were notified of computer randomization after prostate excision. Further continence outcomes were assessed by analysis of Expanded Prostate Cancer Index Composite questionnaire questions 1 and 12, International Prostate Symptom Score and 24-hour pad weights. Statistical significance was defined as $p < 0.05$

Results: A total of 94 patients were randomized, 47 to each arm. Preoperative clinical and functional variables were equivalent between study arms. There were no complications associated with either anastomotic technique. Of the 87 evaluable patients 62 (71.3%) met our 3-month continence definition. The null hypothesis was not rejected as 33 (81%) controls and 29 (63%) posterior rhabdosphincter reconstruction treated patients were continent at 3 months (chi-square $p = 0.07$, Fisher exact $p = 0.1$). Likewise there was no significant difference between arms in 24-hour pad weights ($p = 0.14$), International Prostate Symptom Score ($p = 0.4$), absence of daily leaks ($p = 0.4$) or perception of urinary function ($p = 0.4$).

Conclusions: In this randomized clinical trial posterior rhabdosphincter reconstruction offered no advantage for return of early continence after robotic assisted radical prostatectomy.

Key Words: prostatic neoplasms, prostatectomy, treatment outcome, urinary incontinence, robotics

URINARY continence represents a paramount competitive goal from radical prostatectomy heavily influencing postoperative quality of life.[1,2] Continence outcomes relate to methodological instruments, definitions, preoperative risk factors and pivotal intraoperative factors driven by execution of surgical

0022-5347/11/1854-1262/0
THE JOURNAL OF UROLOGY®

Vol. 185, 1262-1267, April 2011
Printed in U.S.A.
DOI:10.1016/j.juro.2010.11.085

technique.[3] In terms of technique factors investigators have proposed methods of preserving the urethral complex (vascular control, urethral length, neurovascular bundles and puboprostatic ligaments) and keeping pudendal nerve branches intact, or improving the management of the bladder neck (preservation, tubularization, reconstruction and intussusception) to improve continence. In this regard Rocco et al reported on a novel surgical technique for reconstruction of the musculofascial plate that provides support to the posterior periurethral rhabdosphincter.[4] Reportedly this rather simple modification resulted in a significant improvement (greater than 40 %) in continence recovery after open radical prostatectomy. Retrospective investigations evaluating PRR in laparoscopic and robotic assisted radical prostatectomy suggested equally promising results, explained in part by the prevention of caudal urethral retraction and less tension in the anastomosis.[5–7]

It was our impression that potential benefits of this surgical technique warranted rigorous evaluation. We conducted a phase I feasibility trial and noted no adverse events attributed to PRR in 17 patients (internal unpublished data). It became our biased impression that PRR decreased tension and facilitated the vesicourethral anastomosis, which would lead to improved continence for our patients. Therefore, we designed and conducted a single institution phase II surgical trial designed to answer the question of whether PRR reconstruction would improve continence recovery outcomes. Months after accrual completion a prospective RCT evaluating double layer reconstruction which included PRR and puboprostatic collar preservation in a robotic cohort was published.[8] The trial evaluated continence outcomes 1 month after RARP and revealed no differences between arms. We present the results of a prospective RCT evaluating the impact of PRR alone on continence outcomes.

MATERIALS AND METHODS

Enrollment

We designed a prospective RCT for men undergoing RARP at a tertiary referral hospital. Upon review and approval by the George Washington University institutional review board, the trial was opened for accrual on January 7, 2008 and randomization was completed on June 25, 2008. The randomization schema is detailed in figure 1. All RCT 010120 data, including baseline functional, clinical, pathological and outcomes data, were collected by research personnel, and loaded into a custodial electronic registry system. All procedures were performed by 1 of 3 surgeons each operating independently, each with experience in RARP of more than 60 cases by the start of the RCT. The nuances of each procedure were recorded directly by the surgeons immediately after the procedure using electronic

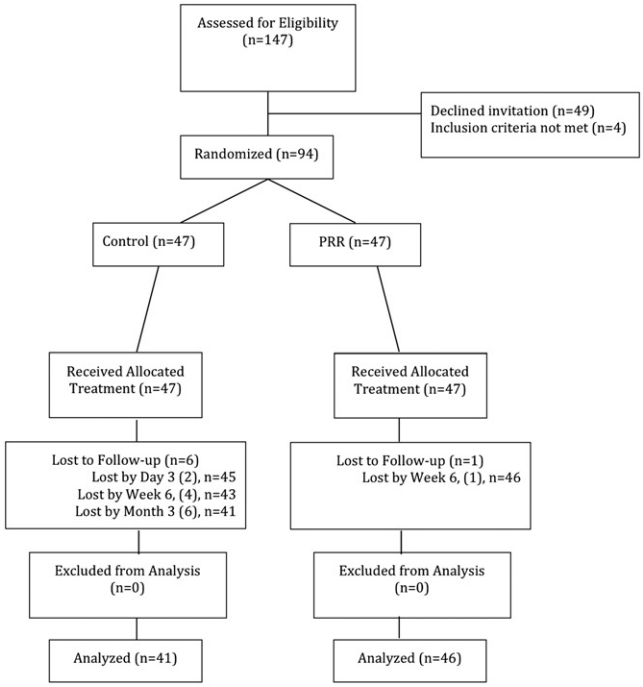

Figure 1. Consort diagram showing randomization and patient flow.

forms. Inclusion criteria were 1) clinically localized T1–T2NxMx or N0M0 biopsy proven prostate cancer, 2) Eastern Cooperative Oncology Group 0 performance status and 3) life expectancy that exceeded 10 years. Exclusion criteria were 1) inability to give informed consent, 2) prostate volume greater than 200 gm on transrectal ultrasonography, 3) prior history of urinary incontinence or bladder dysfunction (eg interstitial cystitis, overactive bladder, detrusor areflexia etc) and 4) prior pelvic radiation, cryoablation or hormonal deprivation. Patients were blinded to group allocation. Informed consent was obtained for all patients.

Surgical Technique and Outcome Measures

Men were randomized to standard running vesicourethral anastomosis (controls) vs PRR followed by standard running vesicourethral anastomosis (PRR treated) after trial consent. Computer randomization was achieved through the link, https://www.random.org/integers/ that generates an integer between 1 and 2 for each subject. Subjects assigned values of 1 vs 2 were assigned to controls vs PRR treated, respectively (fig. 1). A transperitoneal RARP approach was used in each case and the surgeon was notified of patient randomization after completion of the prostatectomy. Three surgeons performed RARP independently within this RCT (JDE 40, FJB 39, HAF 15). Neurovascular bundle preservation to various degrees was performed at the surgeon's discretion, independently, and directed by preoperative clinical and functional assessment. The urethral complex dissection was performed following the surgical principles of 1) preservation of periurethral tissue distal to the apex, 2) minimal manipulation of the urethra and 3) maximization of urethral length. For the control group the urethrovesical anastomosis was performed as

described by Van Velthoven et al[9] with a slight modification in that the posterior urethral sutures were incorporated the distal posterior thick layer of Denonvilliers fascia.[10] The treatment group received PRR followed by urethrovesical anastomosis. The PRR technique followed the surgical principles described by Rocco et al.[4,6] A 20Fr Foley catheter was left in all patients. bPLND was not mandatory for low risk patients, those with prostate specific antigen less than 10 ng/ml, Gleason scores 6 or less and clinical stage T1c/T2a.

In the initial postoperative visit, upon removal of the Foley catheter, all men were instructed and encouraged to perform more than 50 Kegel exercises daily. On each assessment encounter (day 3, 6 weeks and 3 months after catheter removal) patients completed a questionnaire that contained questions 1, 5 and 12 of the urinary domain of the EPIC,[11] and the entire I-PSS and Sexual Health Inventory for Men surveys. In addition, at the 6-week and 3-month postoperative encounters patients still using pads were instructed to provide a dry pad in addition to any pad used in the 24-hour interval before the appointment day (7 am the day before to 7 am the appointment day). A standard metric scale was used for pad weight, which was measured by subtracting the weight of the sample dry pad from the weight of wet pad(s). The validated questionnaires were filled out by patients and compiled by research assistants. Pad weight information was collected and recorded by the nursing staff.

Outcomes Measures and Study End Points

Continence recovery at postoperative month 3 was the study primary end point. We defined continence by a score of 0 or 1 in question 5 of the EPIC urinary domain.[11] Secondary end points included patient self-reported daily leaks (EPIC question 1), self-perception of urinary function (EPIC question 5), I-PSS and 24-hour pad weight.

Power Calculation and Statistical Analysis

The study was designed with intent to treat analysis aimed to detect a 2-sided 25% difference between arms at the 3-month study end point, accounting for a 0.05 alpha at 80% power with an anticipated 10% dropout rate. Statistical analysis was performed using computerized software. Statistical differences for discrete variables were assessed using the chi-square test. Differences in continuous measures were determined using independent t tests with $p < 0.05$ considered statistically significant.

RESULTS

A total of 94 men met eligibility and were randomized. Of these men 47 fell into each arm (fig. 1). All patients who consented to the trial received the intended randomization treatment. As shown in table 1 both study arms had statistically similar cancer and functional characteristics. Surgical execution measurements were similar as 89 (95%) men had nerve preservation procedures, with bilateral nerve preservation performed in 35 (75%) and 38 (81%) of controls and PRR treated arms, respectively ($p = 0.8$). Moreover examination of the prostatectomy specimen revealed organ confined (pT2) prostate cancer in 69 (73%) patients with no differences between arms ($p = 0.3$). Invasion of seminal vesicles was observed in 4 patients, 3 controls and 1 PRR treated. bPLND was performed in 60 men and was positive in 4. There were 34 low risk patients (17 on each arm) who did not receive bPLND. In all patients the Foley catheter was removed between postoperative days 6 and 10. There were no urinary leaks and we observed no complications associated with PRR. Over time 7 patients were dropped from the RCT due to lack of compliance with followup.

Table 1. *Baseline patient characteristics*

	Overall	Controls	PRR	p Value
Age:				0.7
Mean	59.7	60.4	59.9	
Median	60.4	60.4	60.2	
IQR	55.2–65.1	54.9–65.1	56.1–63.4	
Serum prostate specific antigen (ng/ml):				0.3
Mean	5.2	5.6	4.9	
Median	4.6	4.7	4.5	
IQR	3.6–6.9	4.1–7.8	3.3–5.6	
No. biopsy Gleason score (%):				0.2
6	45 (48)	19 (40)	26 (55)	
7	38 (40)	23 (49)	15 (32)	
8–10	11 (12)	5 (11)	6 (13)	
No. clinical stage (%):				0.4
T1c	76 (81)	37 (79)	39 (83)	
T2	18 (19)	10 (21)	8 (17)	
No. preop risk (%):				0.6
Low	42 (45)	19 (40)	23 (49)	
Intermediate	37 (39)	19 (40)	18 (38)	
High	15 (16)	9 (20)	6 (13)	
Transrectal ultrasound vol (gm):				0.9
Mean	38.5	38.7	38.2	
Median	32	33.0	30.7	
IQR	25.3–46.3	28.3–45.8	24.5–46.5	
I-PSS:				0.9
Mean	8	8	8	
Median	6	7	5	
IQR	2–12	2–12	2–11	

Outcomes

A total of 62 (71.3%) of the evaluable 87 patients met our 3-month continence definition. At study end point the null hypothesis was accepted, and 33 (81%) of controls and 29 (63%) of PRR treated patients were continent at 3 months (chi-square $p = 0.07$, Fisher exact $p = 0.1$). Relevant answers to the selected EPIC questions are provided in figure 2. There were no differences at the 6-week and 3-month benchmarks between trial arms (t test $p = 0.3$ and $p = 0.14$, respectively). At 3 months 23 (56%) controls vs 21 (45%) PRR treated patients answered 0 (no pads) to EPIC question 5 ($p = 0.3$). Median pad weight at 3 months for the cohort was 10 gm (IQR

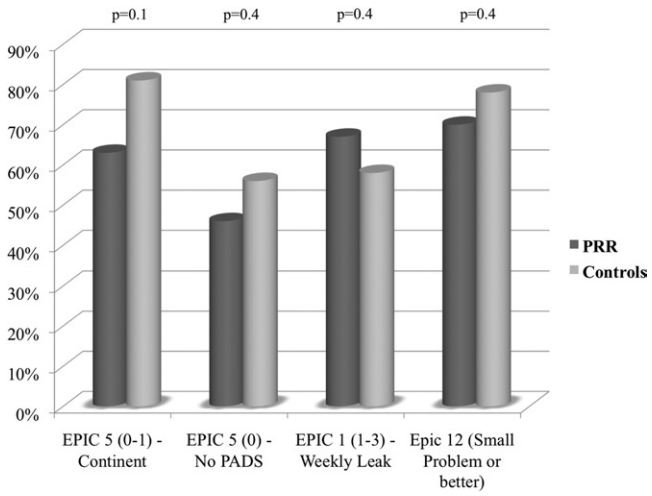

Figure 2. Bars demonstrating patient answers to EPIC questions 1, 5 and 12. EPIC question 5 answers include those who met continence definition and those who were free from pads, with p values at top evaluating significance of differences in answers registered in RCT.

0–78). Pad weight ranged from 3 to 41 gm in the 18 patients using 1 pad daily and less than 20 gm for 2 of the 10 patients using 2 pads daily. Median I-PSS for the RCT cohort was 7 (IQR 4–11). These voiding scores were statistically similar between RCT arms (at 6 weeks p = 0.7 and at 3 months p = 0.4, table 2).

In addition, registered continence outcomes from the 3-day interview and 6-week evaluation were statistically similar between RCT arms. At day 3, 10 (22%) and 5 (11%) controls and PRR treated patients reported 0 to 1 pad (Fisher exact p = 0.16). The respective numbers at week 6 were 18 of 43 (42%) and 19 of 46 (42%, p = 0.9). At day 3, 2 of 45 controls and 1 of 47 PRR treated patients reported absence of daily leaks, yet 20 (44%) controls and 21 (45%) PRR treated patients referred to their urinary function as a small problem or better. By postoperative week 6, 22 of 43 (51%) controls and 26 of 46 (57%) PRR treated patients described urinary function as a small problem or better (p = 0.6). However, 38 (88%) and 40 (87%) controls and PRR treated patients, respectively, reported at least daily leaks (p = 0.8). Both controls and PRR treated patients experienced statistically significant improvement in 24-hour pad weights and I-PSS from postoperative week 6 to month 3 (p <0.01 for both comparisons and RCT arms).

DISCUSSION

Following cadaveric investigation Burnett and Mostwin concluded that stabilization of the rhabdosphincter contained within the male urethral complex was provided by a dorsal musculofascial plate extending the entire length of the rhabdosphincter.[12] Severance of this relatively rigid plate by radical prostatectomy weakens the urethral complex and results in caudal retraction of the urethra.[3,12] These facts of surgical execution led Rocco et al to propose the PRR procedure, "that restores the anatomical and functional length of the rhabdosphincter," which the investigators reported facilitates early recovery of continence from 46% to 86% at 3 months.[4] Subsequent retrospective, neither randomized nor controlled, investigations suggested that PRR held true to its fate.[4–6] Notably the findings of this RCT, the first to our knowledge to strictly evaluate the impact of this technique alone, show that by 3 days, 6 weeks and 3 months after RARP, PRR does not improve continence outcomes (all values p >0.05). Our RCT incorporated a sound objective measurement of pad weight. Likewise, using this metric the 6-week and 3-month outcomes were similar between the randomized arms (p = 0.3 and p = 0.14, respectively).

The lack of benefit conferred by PRR for continence outcomes demonstrated in this RCT was similar to the findings of Menon et al, who conducted a RCT whose treatment arm consisted of anterior reconstruction and PRR.[8] These investigators designed their RCT to detect a 30% 1-month outcomes difference at 90% power and, thus, 116 men were randomized. Using the same continence definition (0 to 1 pad daily) 80% of treated patients vs 74% of controls reached 1-month postoperative continence. They attributed the lack of statistical difference to a better than expected continence rate in the control arm.

In particular we noted the overall 77%, 1-month continence rate reported by Menon et al[8] to be consistent with previous retrospective, nonrandomized, uncontrolled investigations of continence by the same group and others.[13–15] We are unable to substantiate these claims of superior continence following RARP. In this RCT at 6 weeks 49% and 51% of controls and PRR treated patients, respectively, met our continence outcome. The 3-month pad weight analysis revealed that 51% of men did not wear any pads, 20% wore 1 pad daily and 74% of our patients considered

Table 2. *I-PSS and pad weight data*

	No.	Controls Median, Mean (IQR)	No.	PRR Median, Mean (IQR)	p Value
I-PSS:					
3 Days	45	13, 12 (7–15)	47	12, 13 (7–18)	0.8
6 Wks	43	9, 11 (5–15)	46	10, 11 (6–14)	0.7
3 Mos	41	6, 8 (3–12)	46	7, 7 (4–10)	0.4
24-Hr pad wt (gm):					
6 Wks	43	47, 133 (11–195)	46	73, 184 (9–303)	0.3
3 Mos	41	0, 50 (0–15)	46	30, 105 (0–178)	0.14

their urinary function to be a small problem or better. These results are similar to those of previous stringent analysis of postprostatectomy continence by Lepor and Kaci,[16] who observed a 71% 3-month continence rate, and Walsh,[17] who observed that 54% of patients did not use pads 3 months after open radical prostatectomy and 96% were not bothered by urinary function. In addition, similar to our RCT a nonstatistically significant difference favoring no PRR over PRR was noted in a nonrandomized study by Joshi et al.[18] These investigators reported incontinence (defined as any involuntary loss of urine) in 75% vs 69% of no PRR and PRR, respectively, 3 months after surgery ($p = 0.39$). Similarly our RCT demonstrated that 63% of men experienced 1 or more weekly leak episodes at the 3-month end point, without differences between treatment arms. In summary, we advise caution when interpreting the unprecedented 1-month continence rate reported by Menon et al until reproduced by future randomized trials.[8]

Despite the RCT nature of this investigation, certain considerations must be made before interpreting these results. By design and practicality we did not measure the entire urinary function domain nor the entire realm of the EPIC questionnaire. We selected the EPIC questions that we considered most appropriate for the study hypothesis. Therefore, this RCT cannot provide an accurate measurement of urinary specific quality of life associated with PRR or RARP. In addition, we provided instructions to patients for 24-hour pad collection and assume this was performed in accordance. We also did not include routine cystograms in this trial. Therefore, we cannot comment on the effect of PRR on subclinical urinary extravasation at the time of catheter removal, reportedly an advantage of PRR.[8] This study was not double-blinded as the surgeon performing RARP was informed of the patient randomization arm. However, data were obtained and processed by collaborators others than the surgeon. Finally, the roles of surgeon experience and variations on functional outcomes are well established.[19] In this trial 3 surgeons performed 40, 39 and 15 RARPs on the randomized patients. Individual analysis for each surgeon for the 3-month continence outcome did not reveal any significant differences between controls vs PRR treated patients (all values $p > 0.2$).

Notwithstanding the relevant question of our RCT, we believe these results provide an additional meaningful contribution regarding early continence rates after RARP. Some of the marketing and reporting has clouded the introduction and implementation of RARP. In fact, a detailed stringent review by Ficarra et al presented the reported 3-month continence rates ranging between 73% and 93%, allegedly from questionnaires or interviews, using a no pad or a 0 to 1 pad definition of continence, respectively.[14] The findings of this RCT clearly do not support those observations obtained from retrospective, noncontrolled studies.

CONCLUSIONS

Using a continence definition of 0 to 1 pad daily, in our RCT we observed a 3-month continence rate of 71% after RARP and found no difference in continence recovery between RCT arms. While easily reproducible, reconstruction of the musculofascial plate dorsal to the urethra did not provide any advantage that translates into early continence recovery.

REFERENCES

1. Litwin MS, Hays RD, Fink A et al: Quality-of-life outcomes in men treated for localized prostate cancer. JAMA 1995; **273:** 129.
2. Sanda MG, Dunn RL, Michalski J et al: Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008; **358:** 1250.
3. Loughlin KR and Prasad MM: Post-prostatectomy urinary incontinence: a confluence of 3 factors. J Urol 2010; **183:** 871.
4. Rocco F, Carmignani L, Acquati P et al: Restoration of posterior aspect of rhabdosphincter shortens continence time after radical retropubic prostatectomy. J Urol 2006; **175:** 2201.
5. Nguyen MM, Kamoi K, Stein RJ et al: Early continence outcomes of posterior musculofascial plate reconstruction during robotic and laparoscopic prostatectomy. BJU Int 2008; **101:** 1135.
6. Rocco F, Carmignani L, Acquati P et al: Early continence recovery after open radical prostatectomy with restoration of the posterior aspect of the rhabdosphincter. Eur Urol 2007; **52:** 376.
7. Tewari AK, Bigelow K, Rao S et al: Anatomic restoration technique of continence mechanism and preservation of puboprostatic collar: a novel modification to achieve early urinary continence in men undergoing robotic prostatectomy. Urology 2007; **69:** 726.
8. Menon M, Muhletaler F, Campos M et al: Assessment of early continence after reconstruction of the periprostatic tissues in patients undergoing computer assisted (robotic) prostatectomy: results of a 2 group parallel randomized controlled trial. J Urol 2008; **180:** 1018.
9. Van Velthoven RF, Ahlering TE, Peltier A et al: Technique for laparoscopic running urethrovesical anastomosis: the single knot method. Urology 2003; **61:** 699.
10. Eastham JA, Kattan MW, Rogers E et al: Risk factors for urinary incontinence after radical prostatectomy. J Urol 1996; **156:** 1707.
11. Wei JT, Dunn RL, Litwin MS et al: Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology 2000; **56:** 899.
12. Burnett AL and Mostwin JL: In situ anatomical study of the male urethral sphincteric complex:

relevance to continence preservation following major pelvic surgery. J Urol 1998; **160:** 1301.

13. Costello AJ, Haxhimolla H, Crowe H et al: Installation of telerobotic surgery and initial experience with telerobotic radical prostatectomy. BJU Int 2005; **96:** 34.

14. Ficarra V, Cavalleri S, Novara G et al: Evidence from robot-assisted laparoscopic radical prostatectomy: a systematic review. Eur Urol 2007; **51:** 45.

15. Menon M, Shrivastava A, Sarle R et al: Vattikuti Institute Prostatectomy: a single-team experience of 100 cases. J Endourol 2003; **17:** 785.

16. Lepor H and Kaci L: The impact of open radical retropubic prostatectomy on continence and lower urinary tract symptoms: a prospective assessment using validated self-administered outcome instruments. J Urol 2004; **171:** 1216.

17. Walsh PC: Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. J Urol 2000; **164:** 242.

18. Joshi N, de Blok W, van Muilekom E et al: Impact of posterior musculofascial reconstruction on early continence after robot-assisted laparoscopic radical prostatectomy: results of a prospective parallel group trial. Eur Urol 2010; **58:** 84.

19. Bianco FJ Jr, Riedel ER, Begg CB et al: Variations among high volume surgeons in the rate of complications after radical prostatectomy: further evidence that technique matters. J Urol 2005; **173:** 2099.