Age, Obesity, Medical Comorbidities and Surgical Technique are Predictive of Symptomatic Anastomotic Strictures After Contemporary Radical Prostatectomy

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Abbreviations and Acronyms

ASA = American Society of Anesthesiologists

BMI = body mass index

CAD = coronary artery disease

CaPSURE™ = Cancer of the Prostate Strategic Urologic Research Endeavor

DM = diabetes mellitus

EBL = estimated blood loss

HTN = hypertension

LRP = laparoscopic radical prostatectomy

ORP = open radical prostatectomy

PSA = prostate specific antigen

RP = radical prostatectomy

SEER = Surveillance, Epidemiology, and End Results Program

TURP = transurethral resection of the prostate

Purpose: Anastomotic strictures are relatively common after radical prostatectomy and are associated with significant morbidity, often requiring multiple surgical interventions. There is controversy in the literature regarding which factors predict the development of anastomotic strictures. In this study we determined predictors of symptomatic anastomotic strictures following contemporary radical prostatectomy.

Materials and Methods: Between 1999 and 2007, 4,592 consecutive patients underwent radical prostatectomy without prior radiotherapy at our institution. Data were collected from prospective surgical and institutional morbidity databases, and retrospectively from inpatient and outpatient medical and billing records. Cases were assigned a Charlson score to account for comorbidities. Complications were graded according to the modified Clavien classification.

Results: Open radical prostatectomy was performed in 3,458 men (75%) and laparoscopic radical prostatectomy was performed in 1,134 (25%). The laparoscopic radical prostatectomy group included 97 robotic-assisted cases. Median patient age was 59.5 years (IQR 54.7, 64.2). Symptomatic anastomotic strictures developed in 198 patients (4%) after a median postoperative followup of 3.5 months (IQR 2.1, 6.1). On multivariate analysis significant predictors included patient age, body mass index, Charlson score, renal insufficiency, individual surgeon, surgical approach and the presence of postoperative urine leak or hematoma.

Conclusions: Patient factors as well as technical factors influence the development of symptomatic anastomotic strictures following contemporary radical prostatectomy. The impact of these factors is influenced by the individual surgeon and the approach used.

Key Words: prostatic neoplasms, prostatectomy, postoperative complications, contracture

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RADICAL prostatectomy is a well established procedure for the treatment of localized prostate cancer.[1,2] Open RP remains the only treatment modality which has been shown in a randomized controlled trial to reduce metastases and death related to progression of localized prostate cancer.[3] Despite the recent focus on adaptations to the traditional ORP approach, including the introduction of minimally invasive surgical techniques, the success of any treatment for prostate cancer is determined by the 3 key outcomes of oncologic control, return of sexual function and return of urinary function.[4]

Alterations in urinary function after RP are well described, and include the development of anastomotic strictures, also referred to as bladder neck contractures, in addition to prolonged urinary incontinence. A recent analysis of the CaPSURE database, which evaluated RP outcomes in a community setting, reported an anastomotic stricture rate of 8.4%.[5] Similar findings were reported in a SEER-Medicare linked study with anastomotic stricture rates ranging from 5.8% to 14.0% depending on technique.[6] There is wide variation in the published rates of anastomotic stricture following RP, with estimates from as low as 2.7% to as high as 25.7%.[7,8] This wide variation is likely the result of differences in patient populations, surgical practice patterns, postoperative followup and data collection.

Patient factors suggested to predict the development of anastomotic strictures include age, BMI, smoking, HTN, DM and CAD.[5,9] Intraoperative EBL has been suggested to predict the development of anastomotic strictures.[10] Low surgeon volume has been associated with increased rates of complications, including anastomotic strictures, after RP.[7,11] Variations in surgical technique also have a role in the development of obstructive urinary complications, including anastomotic strictures, after RP.[11]

Effective treatment of anastomotic strictures often requires multiple procedures and may lead to urinary incontinence.[5] In fact, on multivariate analysis the development of anastomotic stricture after RP was an independent risk factor for urinary incontinence.[12] Finally, the economic impact of symptomatic urethral and anastomotic strictures in the United States has been documented at more than $6,000 per affected individual.[13]

At our institution demographic, perioperative and postoperative followup data have been continuously recorded in a prospective fashion since 1998 using an institutional database designed for the collection and analysis of clinical outcomes data.[14] Because the development of an anastomotic stricture following RP is an adverse event associated with significant burden, we determined predictors of symptomatic anastomotic stricture in a large, contemporary series of ORP and minimally invasive RP.

PATIENTS AND METHODS

Between January 1999 and June 2007, 4,592 consecutive patients underwent RP without prior radiotherapy for adenocarcinoma of the prostate at our institution. Patients who underwent salvage RP following radiotherapy were not included in the study because this population has significantly higher rates of anastomotic strictures.[15] Data were collected from prospective surgical and institutional morbidity databases. A retrospective review of all inpatient and outpatient billing records, as well as medical records including physician notes, operative notes, discharge summaries, nursing notes and correspondence with local physicians elsewhere was also performed. Institutional review board approval was obtained before commencing the study.

The term symptomatic anastomotic stricture was defined as a narrowing at the vesicourethral anastomosis which prevented passage of a 14.2Fr flexible cystoscope and was associated with obstructive lower urinary tract symptoms. Routine cystoscopy was not performed in patients who had undergone RP. All cystoscopies were performed well outside of the immediate perioperative period, and were performed for indications including decreased urinary stream, increased urinary urgency, increased urinary frequency or other suspicious symptoms. Treatment for anastomotic stricture was varied and patients who chose to not undergo treatment were also included in the study.

The presence of a urinoma or urine leak was defined as evidence of urine extravasation on an imaging study (computerized tomography or cystogram), or a drain fluid creatinine of 1.5 mg/dl or greater (if this was also greater than serum creatinine). The definition of a hematoma included any postoperative bleeding identified in the surgical bed on computerized tomography or significant bleeding noted on surgical re-exploration in the immediate perioperative period. The grade (I, II, IIIa, IIIb, IVa, IVb or V) of the complication was assigned according to the modified Clavien classification.[16]

Data collected included patient age, ethnicity, BMI, clinical stage, biopsy Gleason score, preoperative PSA, ASA physical status classification score and Charlson comorbidity index,[17] prior treatment, RP approach, pathological Gleason score and stage, nodal status, surgical margin status, specimen weight, operative time, EBL, preoperative and postoperative serum hemoglobin, transfusion data, length of stay, and emergency room visits or readmissions at our institution or elsewhere. In total 155 patients, including 140 treated with ORP and 15 with LRP, received salvage radiation at a median followup of 22.8 (IQR 12.9, 36.9) months for ORP and 16.5 (IQR 12.5, 29.7) months for LRP.

Cox proportional hazards analysis was performed using forward step-wise variable selection to obtain maximum likelihood estimates of the hazard ratios and 95% CI. Parameters evaluated as predictors of symptomatic anastomotic strictures included age, BMI, ethnicity, individual comorbidities including diabetes, history of renal disease or insufficiency, Charlson score, ASA score, history of prior TURP, PSA, clinical stage, biopsy Gleason score, specimen weight, EBL, operative time, surgeon,

surgeon experience (captured as case number), and presence of postoperative hematoma or urine leak. Patients were censored at the time of salvage radiation therapy. The analysis was repeated separately for the subsets of patients undergoing ORP or LRP. Statistical analyses were performed using the SPSS® statistical package.

RESULTS

Patient Population

Open RP was performed in 3,458 patients (75%) and laparoscopic RP was performed in 1,134 (25%). The LRP group included 97 robotic-assisted cases. The majority of patients were white (88.6%), with the remainder being African-American (6.9%) or other (4.5%). Median patient age was 59.5 years (IQR 54.7, 64.2). Median BMI was 27.6 kg/m^2 (IQR 25.4, 30.3). Clinical stage was T1 in 2,864 patients (62.4%), T2 in 1,571 (34.2%) and T3 in 150 (3.3%). Biopsy Gleason score was 6 or less in 2,679 patients (58.3%), 7 in 1,544 (33.6%) and 8 or greater in 369 (8.0%). Median preoperative PSA was 5.5 ng/ml (IQR 4.1, 7.8). ASA score was 1 in 501 patients (10.9%), 2 in 3,506 (76.4%), 3 in 580 (12.6%) and 4 in 1 (0.02%). Charlson comorbidity score was 0 in 3,721 patients (81.0%), 1 in 673 (14.7%), 2 in 157 (3.4%), 3 in 33 (0.7%), 4 in 5 (0.1%) and 5 or greater in 3 (0.1%). Common comorbidities included HTN in 1,714 patients (37.3%), dyslipidemia in 1,623 (35.3%), CAD in 328 (7.1%) and DM in 311 (6.8%).

Operative Details

Median operative time was 213 minutes (IQR 176, 255). Bilateral pelvic lymphadenectomy was performed in 4,278 patients (93.2%) and the median node count was 10 (IQR 7, 15). Median EBL was 900 ml (IQR 500, 1,500).

Pathological Findings

Pathological Gleason score was 6 or less in 1,681 patients (36.6%), 7 in 2,489 (54.2%) and 8 or greater in 324 (7.1%). Pathological stage was pT0 in 35 patients (0.8%), pT1 in 3,186 (69.4%), pT2 in 1,272 (27.7%) and pT3 in 99 (2.2%). Nodal status was N0 in 4,060 patients (88.4%), N1-2 in 218 (4.7%) and NX in 314 (6.8%). Seminal vesicle invasion was seen in 302 patients (6.6%) and positive surgical margins were seen in 634 (13.8%). Median specimen weight was 50 gm (IQR 41, 63).

Postoperative Care

Median length of hospital stay was 3 days (IQR 2, 3) and median catheterization duration was 11 days (IQR 9, 15). Prolonged pelvic drainage (greater than 7 days) was observed in 114 patients (2.5%). Drain fluid was sent for creatinine analysis in 775 patients (16.9%) and routine postoperative cystography was performed in 187 patients (4.1%).

Anastomotic Stricture

A symptomatic anastomotic stricture developed in 198 patients (4.3%) after a median followup of 3.5 months (IQR 2.1, 6.1) after RP. Almost all patients (98.6%) had more than 1 month of followup. The grade of the anastomotic stricture was I in 9 patients, IIIa in 81 and IIIb in 108. Predictors of symptomatic anastomotic stricture on multivariate analysis with and without surgeon included in the model are presented in the table. Significant predictors included patient age, BMI, Charlson score, renal insufficiency, individual surgeon, surgical approach and the presence of postoperative urine leak or hematoma.

DISCUSSION

Symptomatic anastomotic strictures developed in approximately 4% of our patient population, which is lower than published population based series,[5,6] but in line with other single center series.[18,19] We have shown that the development of a symptomatic anastomotic stricture following RP is influenced by surgical approach and technique in addition to patient factors.

Individual surgeon experience and technique have been shown influence the development of anastomotic strictures.[7,11] Begg et al evaluated 11,522 men in the SEER-Medicare linked database and noted a lower rate of late urinary complications, the majority of which were anastomotic or urethral strictures, for higher volume surgeons.[11] Hu et al evaluated a later SEER-Medicare linked database to

Predictors of symptomatic anastomotic stricture on multivariate Cox proportional hazards analysis

	Hazard Ratio (95% CI)	p Value
Model with surgeon		
History of renal disease/insufficiency	4.0 (1.2–12.7)	0.020
Charlson score	1.3 (1.1–1.6)	0.005
BMI	1.04 (1.01–1.08)	0.012
Surgeon:		
3 vs 1	5.7 (1.9–17.1)	0.002
5 vs 1	3.3 (1.5–7.2)	0.002
9 vs 1	0.08 (0.01–0.56)	0.012
10 vs 1	3.7 (1.3–10.7)	0.016
11 vs 1	4.3 (2.5–7.2)	<0.001
12 vs 1	9.7 (6.0–15.7)	<0.001
EBL (per 100 ml)	1.03 (1.01–1.04)	0.001
Postop hematoma	4.4 (2.2–8.7)	<0.001
Model without surgeon		
Age	1.03 (1.01–1.05)	0.009
Charlson score	1.3 (1.04–1.5)	0.019
BMI	1.07 (1.03–1.10)	<0.001
Prostatectomy (LRP vs ORP)	0.11 (0.06–0.23)	<0.001
History of renal disease/insufficiency	4.3 (1.4–13.6)	0.013
Postop urinoma/urine leak	2.3 (1.3–3.9)	0.002
Postop hematoma	2.8 (1.4–5.6)	0.005

Analysis included 4,265 cases.

evaluate the difference between minimally invasive and open RP and noted a lower rate of anastomotic strictures in the minimally invasive group (5.8% vs 14.0%, $p < 0.001$).[6] Our analysis also showed that individual surgeon is a predictor of the development of symptomatic anastomotic strictures. This finding is likely related to varying levels of training and experience as well as different technical abilities of the surgeon. In addition, this may be reflective of the different approaches used by individual surgeons. Some surgeons only performed LRP (eg surgeon 9) while the reference surgeon only performed ORP. In our model with surgeon as a variable, age, BMI, Charlson score, EBL and postoperative hematoma were all independent predictors of a symptomatic anastomotic stricture. Surgical approach was the strongest predictor of an anastomotic stricture when the entire cohort was included and without individual surgeon as a variable (LRP vs ORP HR 0.11, $p < 0.001$). Of note, this association appears to be even stronger than that shown by Hu et al.[6]

Because surgical approach was such a strong predictor of the development of a symptomatic anastomotic stricture and because including the surgeon in the multivariate model may have masked other factors related to the development of anastomotic strictures, we also analyzed our data by removing the surgeon as a variable. Using this model age, BMI, Charlson score, history of renal disease, surgical approach and postoperative urine leak or hematoma were all independent predictors of the subsequent development of symptomatic anastomotic strictures. This model may be more applicable to most practicing urologists.

The CaPSURE investigators showed that in a community-wide cohort of 6,597 men, age and BMI were associated with the development of urethral strictures after treatment for prostate cancer.[5] While these investigators evaluated patients treated with RP or radiation therapy and did not differentiate between anastomotic or other urethral strictures, they did show a much higher rate of strictures in men treated with RP than in those treated with other modalities. Therefore, the results of the analysis are likely reflective of anastomotic stricture after RP. Similarly we showed that increasing age and BMI are independently associated with the development of symptomatic anastomotic strictures. Like others we also showed that medical comorbidities, measured in our model with Charlson score, are associated with the development of symptomatic anastomotic strictures.

In a retrospective review of 467 patients Borboroglu et al found a significantly higher incidence of anastomotic strictures in current cigarette smokers (26%), and in patients with CAD (26%), HTN (19%) and DM (21%).[9] An association with longer operative time and higher EBL was also identified. Multivariate analysis identified smoking as the strongest predictor. Surya et al identified prior TURP as another factor predictive of anastomotic stricture following RP.[20] In our analysis prior TURP, CAD, DM and a smoking history were not independently associated with formation of symptomatic anastomotic strictures after RP. However, Charlson score, which includes CAD and DM as components of the score, was associated with symptomatic anastomotic stricture.

Despite the widely accepted belief that anastomotic disruption contributes to the development of anastomotic strictures, there are few studies in the literature to support this. In their series of 1,370 RPs Hedican and Walsh found that anastomotic strictures and long-term incontinence developed in 3 patients treated expectantly for postoperative hemorrhage requiring transfusion.[10] In contrast, mild incontinence only developed in 1 of 4 patients treated with surgical exploration, suggesting that anastomotic distraction by pelvic hematoma may contribute to the development of anastomotic strictures.

Similarly there are few published studies that support an association between anastomotic urine leak and the subsequent development of anastomotic strictures. Surya et al retrospectively evaluated 156 patients who had undergone RP and identified 18 with anastomotic strictures (11.5%).[20] Significant predictors included anastomotic urine leak, excessive blood loss and prior TURP. In contrast, Levy et al found that the identification of contrast extravasation on voiding cystourethrogram at 3 weeks postoperatively did not correlate with the subsequent development of anastomotic stricture, provided that the Foley catheter was left in place until there was documented resolution.[21] We found that postoperative hematoma and prolonged urine leak are independently associated with the formation of symptomatic anastomotic strictures.

Our study does have limitations. Despite the fact that most of the data analyzed in our study came from prospectively maintained databases at our institution, we cannot guarantee that all outcomes data from those patients who chose to be followed elsewhere were accurately captured. In addition, it was difficult to achieve consensus in defining urine leak and urinoma for our patient population. Postoperative care may vary by surgeon, which may lead to differences in the reporting of certain complications such as urine leak or urinoma, where the detection is likely influenced by the threshold at which drain fluid analysis is performed or imaging studies are ordered. Finally, our study reports on complications at a high volume cancer center where many surgeons have subspecialized practices and, therefore, our findings may not be generalizable.

CONCLUSIONS

This study demonstrates that the likelihood of symptomatic anastomotic strictures developing following contemporary RP is multifactorial, and is related to patient and technical factors. Patient factors predictive of the development of symptomatic anastomotic strictures include age, obesity, Charlson score and renal disease. Technical factors include the individual surgeon as well as the surgical approach (LRP vs ORP). Postoperative hematoma and the presence of a urine leak, both presumably related to surgical technique, are also predictive of the formation of symptomatic anastomotic strictures.

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