Oncology

Nerve-sparing Prostatectomy and Urinary Function: A Prospective Analysis Using Validated Quality-of-life Measures

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OBJECTIVES
To prospectively study whether urinary function and bother are directly related to neurovascular bundle preservation at radical prostatectomy using validated quality-of-life questionnaires.

METHODS
A total of 91 consecutive patients undergoing radical prostatectomy were prospectively studied using the University of California, Los Angeles, Prostate Cancer Index and the International Prostate Symptom Score. The patients were divided into 2 groups (>50% nerve sparing vs ≤50% nerve sparing). To control for differences in the 2 groups, linear mixed models were performed to adjust for the time after surgery, preoperative sexual ability, and urinary function.

RESULTS
Of the 91 patients, 62 (68%) had >50% nerve-sparing during prostatectomy. Their mean age at surgery was 59 ± 6 years, and the mean follow-up was 16 ± 9 months. Of the 91 patients, 29 (32%) had ≤50% nerve sparing during prostatectomy. Their mean age at surgery was 64 ± 8 years, and the mean follow-up was 13 ± 7 months. Increased nerve sparing was associated with better urinary function (P = .014) and less urinary bother (P = .043). After adjusting for preoperative variables, the increased nerve-sparing group scored 8.4 points (95% confidence interval 1.3-15.4) higher for urinary function and 8.5 points (95% confidence interval 0.3-16.8) higher for urinary bother compared with the group. The International Prostate Symptom Score improved in both groups of patients, and no significant differences were found between the 2 groups.

CONCLUSIONS
The results of our study have shown that nerve-sparing prostatectomy is associated with improvement in urinary function and bother. This improvement was modest and is of unknown clinical significance. UROLOGY 73: 1336–1341, 2009. © 2009 Elsevier Inc.

Surgical treatment of clinically localized prostate cancer in the modern era has focused on decreasing the morbidity inherent to the procedure. Preservation of the neurovascular bundles (NVBs) during prostatectomy has resulted in improved sexual function postoperatively in large series.1,2 NVB preservation has also been suggested to improve urinary function after radical prostatectomy, but quality prospective data are lacking. In a recent study of nerve-sparing perineal prostatectomy, preservation of the NVBs was thought to confer a significant benefit to continence.3 In 2006, Burkhard et al.4 reported on a series of 536 patients for whom nerve sparing during retropubic prostatectomy was associated with improved continence. However, that study did not use validated surveys and did not validate the success of the nerve-sparing attempts by correlating them with the sexual function data. In addition, multiple surgeons were included during a period in which nerve-sparing techniques changed. A wide variation in postoperative potency after nerve-sparing attempts has been reported,1,5 reinforcing the importance of correlating the sexual function data to ensure that NVB preservation has indeed been successful. Only by demonstrating NVB preservation through sexual function data can we ensure that we are actually testing the hypothesis that NVB preservation affects continence. The precise physiologic mechanism for improved continence is unknown, but several studies have proposed a neural contribution from the NVBs to the sphincteric mechanism.6 Thus, sparing the NVBs during prostatectomy might leave patients with more normal urethral sphincter tone and function. A return of continence has also been shown to be associated with the surgical technique.7 Careful dissection around the apex of the prostate during NVB preservation might better preserve the urethral support and therefore result in improved continence. The purpose of this study was to better assess the effect of NVB preservation on urinary function using prospective data from a series of

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0090-4295/09/$34.00
patients undergoing open nerve-sparing radical retropubic prostatectomy and comparing the findings with those from a non-nerve-sparing cohort.

**MATERIAL AND METHODS**

From January 2002 to January 2005, 91 consecutive patients with clinically localized prostate cancer were enrolled in the present study. The patients were assessed prospectively using the University of California, Los Angeles, Prostate Cancer Index (PCI) and the International Prostate Symptom Score (IPSS). The patients completed the questionnaires preoperatively and at 3, 6, 9, 12, and 18 months postoperatively. No formal selection criteria were used; all patients with clinically localized, low-grade disease were considered candidates for nerve sparing. At surgery, the degree of NVB preservation was recorded by 1 surgeon (C.D.).

For the statistical comparison, the patients were divided into 2 cohorts according to the percentage of nerve sparing: group 1, >50% nerve sparing; and group 2, ≤50% nerve sparing. The outcomes assessed included urinary function, bother, and sexual function from the PCI, as well as the IPSS. Linear mixed modeling was used to analyze urinary function, urinary bother, and IPSSs over time (Statistical Analysis Systems, version 9.1, SAS Institute, Cary, NC). Among the factors considered in the model were age, baseline urinary function, baseline urinary bother, current sexual function, current sexual bother, and interval from surgery to determine differences in function between the 2 groups. The differences were considered statistically significant if the Bonferroni-corrected P value was less than .05.

Open radical retropubic prostatectomy was performed through a lower midline incision in a similar fashion in all patients. The NVBs were separated by incising the lateral prostatic fascia sharply and gently teasing the NVBs off the prostate using blunt and sharp dissection. Before division of the prostatic apex, a plane was developed between the urethra and the NVB. The apical dissection was then performed in such a fashion to spare the maximal sphincter component in the membranous urethra while respecting the prostate margins. The apical urethral dissection procedure was the same for each patient, regardless of the attempt at NVB sparing, and all patients underwent bladder neck reconstruction to approximately 30F. Four monofilament sutures were used for the anastomosis, and a 20F Foley catheter was placed. The catheter was removed 10-14 days postoperatively. Sexual rehabilitation was encouraged in all patients immediately after catheter removal, and the patients were given a prescription for sildenafil 50-100 mg once weekly.

**RESULTS**

The baseline characteristic are listed in Table 1. Of the 91 patients, 62 were in group 1 (>50% nerve sparing), with an average age of 59 ± 6 years and average follow-up of 16 ± 9 months. Group 2 (≤50% nerve sparing) included 29 patients, with an average age of 64 ± 8 years and average follow-up of 13 ± 7 months. Group 2 had a greater percentage of patients with Gleason score ≥8 cancer on the initial biopsy and a greater clinical stage. The difference in pathologic weight was not significant.

Postoperative sexual function was significantly different (P < .001) between the 2 groups (Fig. 1). Greater nerve sparing was also associated with better urinary function (P = .014) and urinary bother (P = .043) with time (Fig. 2). After adjusting for preoperative score, interval from surgery, and current sexual ability, the bilateral NVB sparing group, on average, scored 8.4 points (95% confidence interval 1.3-15.4) more on urinary function and 8.5 points (95% confidence interval 0.3-16.8) more on urinary bother. Both groups had a significant reduction in the IPSS (Fig. 3; P < .001). However, after controlling for preoperative function, interval from surgery, and current sexual ability, the IPSS was not significantly different between the 2 groups (P = .102).

Of the 91 patients, 91% completed ≥4 surveys. Four patients were lost to follow-up. Five patients reported postoperative complications. Of the 91 patients, 2 of the 62 in group 1 and 1 of the 29 in group 2 presented with bladder neck contracture. One patient in each group reported fossa navicularis strictures that were dilated in the clinic.

**COMMENT**

The anatomy and function of the NVB has been investigated, but the results have been difficult to interpret. In 2002, Michl et al. reported that intraoperative nerve stimulation resulted in no measurable changes in the urethral pressure profile using needle electrodes. Conversely, in 2003, using the Cavermap Surgical Aid, Nelson et al. were able to demonstrate consistent increases in urethral pressure in 8 patients with intraoperative stimulation. These studies were limited by technical constraints and difficulty in providing accurate reproducible results.

In the normal male urinary tract, urinary continence is maintained by the bladder neck, prostatic smooth muscle, and external smooth and striated sphincters. The first 2 parts of the continence mechanism are removed at prostatectomy, and only damage to the external sphincter is left to account for incontinence. The sphincter has 2 functional parts: an external striated component innervated by the pudendal nerve and a smooth muscle component with unknown innervation. Experimental paralysis of the pudendal nerve has shown that the striated component alone is incapable of maintaining continence, and the smooth muscle component of the external sphincter appears to be responsible for maintaining the passive control of urine. Careful apical dissection and preservation of the membranous urethral length is important to preserve postoperative urinary continence. Urodynamic analysis has shown intrinsic sphincter dysfunction to be the dominant finding in 88% of patient studies with postprostatectomy incontinence. Sphincteric dysfunction can result in inadequate urethral length or possible damage to the innervation of the smooth muscle component of the sphincter.
A meticulous apical dissection with maximal urethral preservation is technically challenging and might be difficult while respecting surgical margins, especially in men with larger prostate volumes. In men with coexisting benign prostatic hyperplasia, many surgeons believe that apical dissection, as well as NVB-sparing techniques, might not be as high quality as that in men with smaller prostates. Consequently, many surgeons believe that larger prostate volumes lead to poorer continence rates and sexual function outcomes, although series have been published that have disputed these opinions. An additional mechanism that might account for the increased

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>P Value</th>
<th>Group 1 (&gt;50% NS; n = 62)</th>
<th>Group 2 (≤50% NS; n = 29)</th>
<th>All (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>.004</td>
<td>59 ± 6</td>
<td>64 ± 8</td>
<td>61 ± 7</td>
</tr>
<tr>
<td>Preoperative Gleason score (%)</td>
<td>.001</td>
<td>100 (62/62)</td>
<td>79 (23/29)</td>
<td>93 (85/91)</td>
</tr>
<tr>
<td>Clinical stage (%)</td>
<td>.080</td>
<td>61 (38/62)</td>
<td>48 (14/29)</td>
<td>57 (52/91)</td>
</tr>
<tr>
<td>Pathologic stage (%)</td>
<td>.072</td>
<td>89 (54/61)</td>
<td>72 (21/29)</td>
<td>83 (75/90)</td>
</tr>
<tr>
<td>Baseline urinary function score</td>
<td>.468</td>
<td>58</td>
<td>28</td>
<td>86</td>
</tr>
<tr>
<td>Baseline urinary bother score</td>
<td>.119</td>
<td>92.3 ± 11.7</td>
<td>90.2 ± 14.1</td>
<td>91.6 ± 12.5</td>
</tr>
<tr>
<td>Baseline IPSS</td>
<td>.252</td>
<td>54</td>
<td>28</td>
<td>82</td>
</tr>
<tr>
<td>Baseline sexual function</td>
<td>.450</td>
<td>58</td>
<td>27</td>
<td>85</td>
</tr>
<tr>
<td>Pathologic weight (g)</td>
<td>.355</td>
<td>62</td>
<td>29</td>
<td>91</td>
</tr>
</tbody>
</table>

NS, nerve sparing; IPSS, International Prostate Symptom Score.
incontinence postoperatively in men with large obstructive prostates is bladder instability, which is commonly found after prostatectomy.14,18

In 2006, Burkhard et al.7 suggested that NVB sparing affects the continence rates in series of 536 men after radical prostatectomy. That series demonstrated that postoperative urinary continence is highly associated with a NVB-sparing technique, although the study had several weaknesses. First, no correlation with sexual function data was done. Because nerve-sparing quality is highly variable and detailed anatomic studies demonstrating NVB preservation are not possible, we must use sexual function data as a surrogate measure of the success of nerve preservation. Second, their study did not use validated questionnaires in a prospective fashion to collect objective data. Data collected in a prospective fashion using objective measures should be considered more robust. The investigators also did not address the possibility that bladder instability and prostatic size influenced their results. Finally, multiple surgeons were included, and the study was performed during period when nerve-sparing techniques were evolving.

In our series, we collected prospective data on patients’ quality of life using validated questionnaires to assess urinary and sexual function. We believe correlation with sexual function data is essential to establish whether attempts at NVB preservation were successful. The groups shown in Figure 1 were significantly different statistically and their postoperative function reflects the accuracy of the assessment of the nerve-sparing estimation. The observed difference in preoperative sexual function between the 2 groups most likely reflects a selection bias with regard to the attempt to spare nerves in patients with severe erectile dysfunction. Statistical models were created to correct for the observed differences in patient groups before analysis.

Our data set used a single surgeon, who estimated the degree of nerve sparing and performed a similar apical dissection in all patients. The pathologic prostate volume was recorded and was not significantly different between the 2 groups. Although the sample size in our study was comparatively small, we used validated prospective quality-of-life measures and analyzed our data in a rigorous fashion. In addition, 91% of our patients completed ≥4 questionnaires.

The baseline age and biopsy Gleason score were different between the 2 groups. Age at prostatectomy is frequently cited as an important variable in urinary and sexual function and should be considered in the evaluation of models for quality of life after surgery. Although single-surgeon series offer the theoretical advantage of less technical variation, we acknowledge that it is not possible to keep the surgeon completely unaware of the disease stage and grade. This information could potentially influence surgical decisions and possibly the endpoints of our study.

The PCI has multiple domains, including urinary function and bother. The urinary function domain comprehensively addresses leakage issues, including pad use, but also the more subtle aspects of incontinence, including dribbling and leaking. It is highly reliable, consistent, and easily understood by patients.19 In our study, although good urinary function and continence were achieved in both groups, significant differences between groups were reported in urinary function and bother using the PCI. Urinary function and bother improved by 8.4 and 8.5 points, respectively. Although this was not a large change, differences of 5-10 points on a 100-point scale are thought to be clinically meaningful.20,21 We also observed an improvement in IPSS in both groups, but we were unable to show a significant difference among the varying degrees of NVB preservation. If a difference had been found between our 2 groups, one could hypothesize that bladder outlet obstruction and intrinsic bladder function play a key role in the differences seen in the urinary domains of the PCI.

Our study has contributed to the small body of evidence that NVB is associated with some improved urinary function. The observed improvement appears to be modest, and it is clear that NVB preservation is not essential for good continence outcomes. To our knowledge, this is the only study that has correlated the degree of nerve sparing with the sexual function data and attempted to exclude any bias resulting from size, preoperative function, and bladder instability. In addition, we believe that a study using a single surgeon avoids the bias of obvious differences in technique that could influence the data.

**CONCLUSIONS**

Most of men undergoing nerve-sparing and non-nerve-sparing prostatectomy can achieve high rates of continence and urinary function. After multivariate analysis controlling for preoperative variables, nerve-sparing prostatectomy appears to be associated with a modest improvement in urinary function and bother, as reported using validated patient questionnaires.
The article by Abel et al. revalidates the observation that nerve sparing during radical prostatectomy is associated with better recovery of urinary continence. The association of nerve sparing with better continence recovery was first observed in a retrospective chart review study, was soon thereafter corroborated by a prospective study of patient-reported outcomes, and eventually was ascertained in the setting of perineal prostatectomy. Recently, a prospective study using a validated health-related quality-of-life instrument extended the validation of nerve-sparing benefit to a multicenter setting that included laparoscopic and robot-assisted prostatectomy.

The authors question whether the nerve-sparing benefit to urinary continence recovery is clinically meaningful, because the urinary health-related quality-of-life score differences, that they deemed attributable to nerve sparing, were modest. However, the authors’ own observation, that the urinary bother scores paralleled concurrent differences in the urinary function scores, suggests that the difference in urinary outcome was indeed clinically meaningful (an associated difference in urinary bother would not be expected if functional incontinence were not clinically meaningful). Health-related quality-of-life outcomes can be made more transparent and clinically interpretable by concurrently reporting the proportion of subjects who reported moderate or worse bother related to a specific domain (eg, urinary bother). Additional insight regarding clinical significance would have been evident had Abel et al. reported the frequency at which patients reported moderate to large urinary problems (in response to the University of California, Los Angeles Prostate Composite Index bother question), stratified by nerve-sparing status.

Insight regarding the mechanisms whereby nerve-sparing might lead to improved continence recovery was recently provided through a separate and elegant study that combined patient-reported outcomes methods with prospective neurophysiologic testing. Catarin et al. found that the pudendal-anal and pudendal-urethral reflexes were unchanged from before to after prostatectomy, demonstrating routine preservation of afferent and efferent pudendal innervation. However, autonomic afferent denervation was common overall (observed in 77% of the entire prostatectomy study cohort), and was evident in 92% of those reporting incontinence (as defined by strict, validated questionnaire criteria). Conversely, prostatectomy patients in whom autonomic afferent innervation was preserved were usually continent. These findings from Catarin et al. provide physiologic evidence supporting a role for the urethral branch of the autonomic, inferior hypogastric plexus that innervates the mucosal and smooth muscle components of the membranous urethra.