

## Laparoscopic Prostatectomy for Severely Symptomatic, Treatment-Refractory Chronic Prostatitis: Preliminary Observations from an Ongoing Phase II Clinical Trial

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Submitted November 3, 2010 - Accepted for Publication February 23, 2011

### ABSTRACT

**INTRODUCTION:** We report outcomes 1 year after surgery for the first 6 consecutive patients enrolled in an ongoing, prospective, Phase II clinical trial of laparoscopic radical prostatectomy (LRP) as a treatment for severely symptomatic, treatment-refractory chronic prostatitis. The protocol is approved by the Western Institutional Review Board and listed on the searchable National Institutes of Health clinical trials Web site.

**METHODS:** Patients met prespecified eligibility criteria, were fully counseled before treatment, gave written informed consent, had surgery, and were regularly monitored after treatment. The primary outcome measure was symptom severity, which was measured prior to LRP and at 1, 3, 6, and 12 months after treatment using the Chronic Prostatitis Symptom Index (CPSI). The exact Wilcoxon signed rank test was used to compare pretreatment and 6-month posttreatment scores, with statistical significance at  $P < .05$ . Patients also described symptoms that were not included on the CPSI. Intraoperative and postoperative complications were recorded.

**RESULTS:** Average patient age was 48.5 years (range, 31-61 years). The pretrial median disease duration was 6.5 years (range 3-31 years). Aside from their prostatitis, all patients were generally healthy. All patients had failed numerous medical, surgical, and complementary treatments. LRP was uncomplicated. All patients reported resolution of their prostatitis. Median CPSI scores were 35 before surgery and 26, 15.5, 10, and 7.5 at 1, 3, 6, and 12 months after surgery, respectively. The 6-month CPSI scores were significantly lower than the preoperative scores ( $P = .03$ ).

**CONCLUSIONS:** Preliminary data suggest that LRP may offer a previously unavailable level of relief for carefully selected patients with severely symptomatic, treatment-refractory chronic prostatitis. This potential needs to be further validated and more thoroughly characterized.

**KEYWORDS:** Chronic prostatitis; Laparoscopic radical prostatectomy; Clinical trial

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**CITATION:** *UroToday Int J.* 2011 Apr;4(2):art 30. doi:10.3834/uij.1944-5784.2011.04.12

### Abbreviations and Acronyms

CPPS, chronic pelvic pain syndrome  
CPSI, Chronic Prostatitis Symptom Index  
LRP, laparoscopic radical prostatectomy  
NIH, National Institutes of Health

### INTRODUCTION

Prostatitis annually accounts for an estimated 2 million outpatient visits in the USA. It is one of the most common disorders seen in urology practices. Of the 4 categories of prostatitis, chronic prostatitis/chronic pelvic pain syndrome

(CPPS) is the most frequently diagnosed; it is thought to account for 90-95% of cases among all prostatitis categories [1].

Chronic prostatitis/CPPS is characterized by episodic and potentially very intense organ-specific complaints that include

perineal pain, urinary burning, and pain upon ejaculation. As with other chronic pain conditions, it is also associated with nonorgan-specific complaints, including fatigue, irritable bowels, and depressed mood. In patients with severe forms of the disorder, symptoms can be durable and ruinous to the patient's quality of life because they may interfere with virtually all physical, emotional, cognitive, and social functions.

The relief afforded by most treatments for chronic prostatitis/CPPS is disappointing. Standard first-line treatment is antibiotic therapy;  $\alpha$ -blockers are also commonly prescribed. However, many patients receive no relief at all from such therapy, or their relief may be only temporary. Indeed, some first-line forms of treatment offer little if any benefit when compared with a

placebo (see Table 1) [2-11]. Subsequently proposed treatments may be minimally more effective; organ-specific treatments such as saw palmetto, finasteride, and prostate massage appear to have little advantage over nonorgan-specific treatments such as placebo, pollen extract, and global massage. Consequently, patterns of care vary and are essentially arbitrary. A substantial and frustrated subset of patients with severe chronic prostatitis/CPPS spends years seeking relief using a broad range of conventional and alternative therapies.

Because chronic prostatitis/CPPS has defied attempts to identify an easy, effective, evidence-based treatment algorithm, professional societies have not issued meaningful clinical guidelines. The European Association of Urology revised its

Table 1. Summary Data From Randomized, Controlled Trials and Case Series Reporting Outcomes of Various Treatments for Patients With Chronic Prostatitis/Chronic Pelvic Pain Syndrome.

doi: 10.3834/uij.1944-5784.2011.04.12t1

Study type / authors	Year of publication	Therapeutic intervention	Median age of patients (yr)	Time from diagnosis to intervention (yr)	Previous treatments	Follow-up (months)	CPSI score			Percentage of patients non-responsive to intervention (%)	Comments
							Baseline	End	Change		
<i>Randomized controlled trials</i>											
Alexander et al. <sup>2</sup>	2004	Placebo	42.6	6.7	Not collected	1.5	25.0	21.6	3.4	78	Inclusion criteria required CPSI score $\geq$ 15; authors referred to this level of symptoms as "moderate." Ciprofloxacin and tamsulosin performed no better than placebo.
		Ciprofloxacin	45.9	6.7			24.2	18.0	6.2	78	
		Tamulosin	45.3	6.3			24.6	20.2	4.4	76	
Ateya et al. <sup>3</sup>	2006	Antibiotics $\pm$ prostate massage	35.3	0	0	> 4	25.0	12.5	12.5	13.5	All patients were treatment-naive; failures were defined by a drop in the CPSI score of < 25%; prostate massage did not affect outcome
Wagenlehner et al. <sup>4</sup>	2009	Placebo	39.3	4.4	46%	3	20.31	14.94	5.91	51.5	Failure was defined by a drop in CPSI score of 25% or at least 6 points; pollen group had a 70.6% response as compared to a 50% response in the placebo group
		Pollen extract	39.7	4.9	41%		19.18	11.72	7.46	30.9	
Shoskes et al. <sup>5</sup>	1999	Placebo	43.5	>0.5	NA†	1	20.2	18.8	1.4	82	Quercetin failures excluded; Failure was defined by a reduction in CPSI of < 75% of baseline score; placebo demonstrated a 20% reduction in CPSI score from baseline.
		Quercetin	46.2	>0.5			21.0	13.1	7.9	33	
FitzGerald et al. <sup>6</sup>	2009	Myofascial physical therapy	43	<3	>1	3	33.5	19.2	14.3	36	Data from male subset of two-gender study; 62% of eligible patients refused to participate; responses classified as "markedly improved" or "moderately improved"; excluded previous failed treatments with myofascial therapy
		Global therapeutic massage	43	<3			25.8	18.2	7.6	60	
Kaplan et al. <sup>7</sup>	2004	Saw Palmetto	42.9	<0.5	All received antibiotics; 82% received alpha blockers	12	24.7	24.6	0.1	NA†	Response to finasteride was measurable in pain and quality-of-life domains but not urinary domain.
		Finasteride	43.5	<0.5		12	23.9	18.1	5.8	NA†	
<i>Case series</i>											
Shoskes et al. <sup>8</sup>	2010	UPOINT	46	2*	1-4	50*	25.2	13.2	12	16	Success was defined as a reduction of $\geq$ 6 points in the CPSI score.
Guercini et al. <sup>9</sup>	2002	Injections	38	5.3#	Repeated antibiotics	12	25	17	8	13	Failure defined by patient judgment of "percent overall improvement" of 0 to 30%
Anderson et al. <sup>10</sup>	2010	Myofascial prostate therapy + relaxation	49	4.25	"Severely refractory"	3-42	25.3	18.7	6.6	11	Success was defined as a reduction of $\geq$ 6 points in the CPSI score
Antolak & Antolak <sup>11</sup>	2008	Pudendal decompression	NA†	NA†	NA†	12	31.6	23.3	8.3	44.6	Analysis censors the 44.6% who were not "cured or significantly improved." Failures include 13.6% who became more symptomatic with treatment.

\*Median #Mean †NA = Not available

guideline in 2009; that guideline is limited to the use of antibiotic therapy [12]. A guideline issued in the UK in 2008 [13] states bluntly that, "There are no reliably effective treatments for chronic prostatitis/CPSP." The American Urological Association offers no clinical practice guideline at all [14].

In 2007, a 55-year-old male was referred by a urologist colleague. The patient had an 8-year history of severe, treatment-refractory chronic prostatitis/CPSP characterized by an inability to comfortably urinate, ejaculate, and sit without a donut cushion. He also had irritable bowels, depression, and social isolation. He had diligently but ineffectively sought relief elsewhere. His prior treatment had included many of the forms of therapy indicated above. As a treatment of last resort, the patient requested and (after extensive discussion) received an uncomplicated laparoscopic radical prostatectomy (LRP) that produced a histologically benign prostate. LRP, which is commonly used to treat asymptomatic prostate cancer, involves removal of the entire prostate with its capsule and both seminal vesicles.

LRP brought this patient immediate and complete relief of all of his complaints. His relief has endured through more than 3 years of observation. He reports normal urinary function, normal erections, and a sex life that was improved by elimination of pain.

We were unaware of any similar case in the literature and we recognized the need to identify possible new treatment strategies for patients with severe, treatment-refractory chronic prostatitis/CPSP. Therefore, our immediate objective was to study other patients with this condition in order to: (1) characterize symptom severity following LRP using a standardized prostatitis symptom measure, (2) record other symptoms as described by the patients, and (3) record intraoperative and postoperative complications.

## METHODS

### *Participants*

Patients were selected from those enrolled into a prospective, Phase II clinical trial that is approved by the Western Institutional Review Board and listed on the searchable National Institutes of Health (NIH) clinical trials Web site [15]. Patients are self-referred or referred by their treating physicians specifically for this trial. Most applicants make initial inquiry remotely by telephone and/or email; no record is kept of possibly eligible applicants who make informal inquiry but do not participate. To be included in the trial, applicants must meet criteria that include illness duration of at least 1 year, age over 30 years, and symptom severity of at least 25 on the validated NIH Chronic

Prostatitis Symptom Index (CPSI). Patients who cannot tolerate anesthesia or speak English are not eligible.

### *Procedures*

Each patient was fully counseled prior to surgery and gave informed consent. Each patient received LRP according to procedures described previously [16] and was carefully monitored following treatment. The primary outcome measure was symptom severity, which was measured prior to LRP and at 1, 3, 6, and 12 months after treatment using the CPSI. The exact Wilcoxon signed rank test was used to compare pretreatment and 6-month posttreatment scores;  $P < .05$  was considered statistically significant. Comparisons with other follow-up evaluations were not undertaken because of the possibility of a type I error. Patients also described any symptoms that were not included on the formal scale. Intraoperative and postoperative complications were recorded.

## RESULTS

### *Patient Characteristics*

We report outcomes for the first 6 patients enrolled in the trial. Race or ethnicity was self-reported as 5 Caucasians and 1 African American. Their median age was 48.5 years (range, 31-61 years). The patients had prostatitis for a median of 6.5 years (range, 3-31 years) at the time of LRP. Aside from chronic prostatitis/CPSP, they were generally healthy. All patients who entered the trial completed follow-up for 1 year after LRP; there were no missing data.

Before LRP, the patients complained of perineal, scrotal, groin, back, urethral, and/or armpit pain as well as weakness, fatigue, malaise, generalized aches, irritable bowels, depression, impaired cognition, and impaired social interactions. Before applying to participate, they had each consulted up to 20 urologists, psychiatrists, chiropractors, orthopedists, hypnotherapists, physical therapists, internists, and/or acupuncturists. As expected in such a patterns-of-care cohort, these patients had a very broad range of diagnostic tests (eg, cystoscopy, ultrasound, serum prostate-specific antigen testing); the tests had not led to effective treatment.

All patients had received numerous and prolonged courses of oral, intravenous, and/or intraprostatic antibiotics and many other treatments:  $\alpha$ -blockers, 5 $\alpha$ -reductase inhibitors, anti-inflammatory medications, benzodiazepines, narcotics, over-the-counter supplements, intraprostatic steroid injections, whirlpool therapy, and physical therapy. All had diagnostic and/or therapeutic prostate massage and all had previous surgery, including: 3 epididymectomies, 1 orchiectomy, 1 urethral dilation, 1 transurethral microwave prostate treatment, 1

transurethral incision of the prostate, 1 bladder neck incision, 1 transurethral prostatectomy, and 1 lumbar fusion with subsequent removal of hardware. Reported complications included anxiety, discomfort, pain, diarrhea, indigestion, stupor, and impaired balance. All expressed frustration with their care.

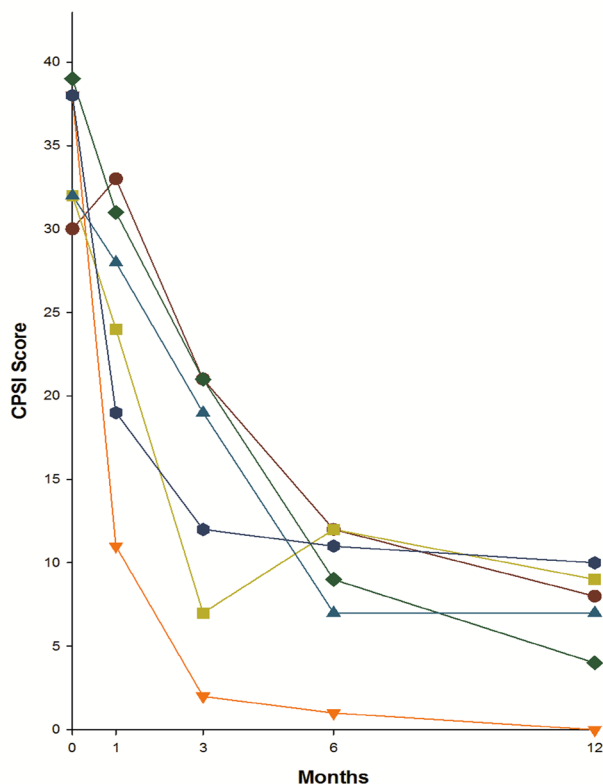
### Treatment Outcomes

Surgery was uncomplicated and produced grossly and histologically unremarkable prostates. We found scars from previous surgery and organ-confined foci of prostate adenocarcinoma (with Gleason scores 5 and 6) in 4 out of the 6 patients.

All patients reported resolution of their prostatitis. CPSI scores declined over time (Figure 1). Median CPSI scores were 35 before surgery and 26, 15.5, 10, and 7.5 at 1, 3, 6, and 12 months after surgery, respectively. The 6-month scores were significantly lower than the preoperative scores ( $P = .03$ ).

Figure 1. CPSI Scores of Individual Patients at Baseline and for up to 12 Months Following Laparoscopic Radical Prostatectomy.

doi: 10.3834/uij.1944-5784.2011.04.12f1



In parallel with CPSI-standardized symptom measures, at 1 year after surgery patients reported resolution of associated fatigue, irritable bowels, generalized aches, and impaired cognition. Five patients reported full continence and 1 patient reported partial continence. Recovery of erectile function was variable at 1 year and seemed to be related to patient age; younger patients recovered erectile function faster and more fully than older patients.

### DISCUSSION

When compared with other patients that are described in the medical literature, the patients with chronic prostatitis/CPPS that were included in this trial are among those with the most: (1) severe or chronic symptoms, (2) disabling conditions, and (3) resistance to traditional treatments. As such, one might expect them to be the least likely to report relief with any new treatment. The observation that they all found substantial relief with LRP is striking and similar to the results of the pretrial individual case. The results raise the specific expectation that a subset of the heterogeneous mix of otherwise treatment-resistant patients with chronic prostatitis/CPPS may find some relief with LRP. Given the general dismal situation for patients with severe, treatment-refractory chronic prostatitis/CPPS, we believe this to be a unique and important initial finding.

Apart from a randomized treatment trial, appreciation of the potential role of LRP in the treatment of severe, treatment-resistant chronic prostatitis/CPPS requires careful comparison of the outcomes of the present patients to the outcomes of other patients receiving standard treatments. However, direct comparison is difficult because of differences in symptom severity, time from diagnosis to treatment, number of treatment failures, trial design, analytical methods, and treatment choice. Specifically, this trial is different from earlier studies in several key aspects (see Table 1). First, the baseline CPSI scores indicate that our patients were among the most severely symptomatic patients ever described. Most of our patients waited a long time from initial diagnosis to treatment and failed what may be the largest number of proposed treatments. Second, we used a clinical intervention that has never been evaluated. Third, the response to treatment (a 27.5-point reduction in median symptom score at 12 months after surgery) was far greater than any previously described. This level of response in such severely symptomatic, treatment-refractory patients was surprising even to the investigators; it appears to set the therapeutic potential of LRP apart from that of other treatments.

This preliminary description of an innovative approach to the management of select patients with severe, treatment-refractory chronic prostatitis/CPPS has numerous limitations

with regards to general application. Like other studies, this trial included patients with a heterogeneous mix of prior treatments, which is a general problem of chronic prostatitis research that interferes with strict comparisons. The trial also had varied (albeit extended) times from diagnosis to treatment. This makes it impossible to know whether LRP might be more or less effective in select subpopulations of patients that are defined by failure to respond to prior specific treatments and/or symptomatic for specific time intervals. Because of its small size (to date) and because enrollment was limited to English-speaking patients, the trial also has limited generalizability.

The trial provides no insights regarding the etiology or type of pain represented by severe, treatment-resistant chronic prostatitis (eg, inflammatory vs. neuropathic). Because LRP removes both the prostate and the seminal vesicles, it does not clarify which organ is involved. Perhaps the only pathophysiological implication is that because LRP provided symptom relief in 3 patients who had failed transurethral procedures, their symptoms did not originate in the transition zone of the prostate and/or the urethra.

The present trial also raises questions about the assessment of symptoms of chronic prostatitis/CPPS. For example, the CPSI includes a measure of perineal pain but no measure of fatigue, generalized aches, cognitive impairment, and/or some of the other associated dimensions of severe, treatment-refractory chronic prostatitis/CPPS that patients reported as resolved after LRP. On its high end, the CPSI appears to under-measure symptoms and treatment effect. Conversely, on its low end, the CPSI may over-measure symptoms because 12 months after LRP, 5 out of 6 patients had measurable CPSI scores even though they all categorically reported that their prostatitis had resolved.

Because many patients informally reported resolution of their fatigue, irritable bowels, and depression, one may hypothesize that the organ-specific and nonorgan-specific symptoms of chronic prostatitis/CPPS all originated in the prostate and/or seminal vesicles. This is a testable hypothesis that correlates with the growing notion that in chronic pain conditions (eg, interstitial cystitis), organ-specific complaints initiate a sequence of events that subsequently come to encompass nonorgan-specific complaints (eg, irritable bowel). Specifically, the observations and informal patient reports suggest that nonorgan-specific complaints are not only secondary to organ-specific complaints but also reversible.

Optimal application of LRP will require good understanding of the likelihood of relief, which is not yet possible. The uniformity of response observed to date in this small series of patients is unlikely to persist, and generalizability has not been studied.

Future research will also require accounting for infertility, treatment risks, and functional recovery that may take longer than 12 months. The point at which LRP becomes a reasonable option will thus reflect a mix of symptom severity, the degree of bother associated with the symptoms, personal valuations, and the probability of success, infertility, and risk.

At this time, any decision to seek or propose LRP as a possible treatment for severe, treatment-refractory chronic prostatitis/CPPS should be made with complete recognition that the observations reported here are preliminary results of a few cases and that there is little knowledge of the durability of symptomatic relief beyond 1 year. Because other treatments are generally cheaper and safer, use of LRP should be seen as potentially appropriate as a treatment of last resort for those patients who have failed many other options. Still, for carefully selected patients whose quality of life is clearly very low and who have failed other treatments, this trial suggests that LRP may offer symptomatic relief. It is our intention to better characterize the effect of LRP on the symptoms of severe, treatment-resistant chronic prostatitis and to report the results of a larger series of patients in the future.

## ACKNOWLEDGMENTS

E. Michael D. Scott and Heather Rohan provided scientific, editorial, and administrative guidance; Hope and Ruth supported trial participants.

**Conflict of Interest:** None declared.

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