Clinical Phenotyping of Patients With Chronic Prostatitis/Chronic Pelvic Pain Syndrome and Correlation With Symptom Severity

Daniel A. Shoskes, J. Curtis Nickel, Robert Dolinga, and Donna Prots

OBJECTIVES To propose a clinical phenotype system (urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness [UPOINT]) to classify patients with urologic pelvic pain to help understand the etiology and guide therapy. We wished to validate this system in men with chronic pelvic pain syndrome (CPPS). CPPS is a heterogeneous syndrome with a variable treatment response.

METHODS A total of 90 men with CPPS were retrospectively classified in each domain of our UPOINT system and the symptoms were measured using the Chronic Prostatitis Symptom Index.

RESULTS The percentage of patients positive for each domain was 52%, 34%, 61%, 16%, 37%, and 53% for the urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness domains, respectively. Of the 90 patients, 22% were positive for only 1 domain, and a significant stepwise increase was found in the total Chronic Prostatitis Symptom Index score as the number of positive domains increased. A symptom duration of >2 years was associated with an increase in positive domains (2.9 ± 0.21 vs 2.3 ± 0.14, $P = .01$). Comparing the total Chronic Prostatitis Symptom Index score with the presence of each domain revealed significantly increased symptoms in patients positive for the urinary, psychosocial, organ specific, and neurologic/systemic domains. When this analysis was repeated for the pain subscore, the psychosocial, neurologic/systemic, and tenderness domains had significantly greater scores. Only the psychosocial and neurologic domains influenced the patients' quality of life.

CONCLUSIONS Applying the UPOINT system to patients with CPPS can discriminate clinical phenotypes, allowing for hypothesis testing for etiology and therapy. The number of positive domains correlated with symptom severity and a longer duration of symptoms increased the number of positive domains. Because each domain has specific targeted therapies, we propose that multimodal therapy might best be guided by the UPOINT phenotype. UROLOGY 73: 538–542, 2009. © 2009 Elsevier Inc.

Category III prostatitis, also known as chronic prostatitis/chronic pelvic pain syndrome (CPPS) is a common condition with a significant affect on quality of life. This clinically defined syndrome has a multifactorial etiology and seems to respond best to multimodal therapy.[1,2] Large multicenter trials of promising treatments have often shown minimal or no benefit compared with placebo; however, the heterogeneous nature of the patients in these studies might have prevented a positive result for patients with the appropriate mechanism or etiology of symptoms. This would be analogous to testing an effective migraine drug in patients only defined as having a headache, which could include patients with a brain tumor, infected tooth, or neck spasm. Currently, we do not have validated biomarkers that would allow us to classify patients in a way that could guide therapy.

In response to this situation, we have proposed a 6-point clinical phenotyping system to classify patients with chronic pelvic pain (CPPS and interstitial cystitis) and to direct appropriate therapy.[3] The clinical domains are urinary symptoms, psychosocial dysfunction, organ-

D. Shoskes is a paid consultant to Farr Labs and a stock holder in Triurol; J. C. Nickel has received grants/research support/scientific study from GlaxoSmithKlein, Merck, Ortho-McNeil, Stellar, Watson Pharmacueticals, Allergan, American Medical Systems, and Pfizer and is a consultant to Farr Laboratories, Merck-Frosst Canada, Ortho-McNeil, Glaxo-Smith-Kline, Triton Pharma, and Watson.

From the Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio; and Queens University, Kingston, Ontario Canada

Reprint requests: Daniel Shoskes, M.D. Glickman Urological and Kidney Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk A100, Cleveland, OH 44195.

Submitted: July 22, 2008, accepted (with revisions): September 10, 2008

0090-4295/09/$34.00
doi:10.1016/j.urology.2008.09.074

Table 1. Domains of UPOINT classification and typical inclusion criteria for each

Urinary
Chronic Prostatitis Symptom Index urinary score >4
Patient complaint of bothersome urgency, frequency, or nocturia
Postvoid residual urine volume >100 mL
Psychosocial
Clinical depression
Evidence of catastrophizing (helplessness, hopelessness)
Organ specific
Specific prostate tenderness
Leukocytosis in prostatic fluid
Hematospermia
Extensive prostatic calcification
Infection
Excluding patients with clinical category I or II prostatitis
Gram-negative bacilli or Enterococcus localized to prostatic fluid
Neurologic/systemic conditions
Pain beyond abdomen and pelvis
Irritable bowel syndrome
Fibromyalgia
Chronic fatigue syndrome
Tenderness of skeletal muscles
Palpable muscle spasm or trigger points in abdomen and pelvic floor

UPOINT, urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness.

specific findings, infection, neurologic/systemic, and tenderness of muscles (UPOINT). Each domain has been clinically defined, linked to specific mechanisms of symptom production or propagation, and associated with specific therapy. The criteria for inclusion into each domain for men with CPPS are summarized in Table 1. This phenotype is qualitative, with each domain scored as yes or no. Symptom severity is then measured using a validated instrument. The UPOINT system has suitable plasticity and adaptability to new data such that biomarkers and treatments can be added as they are validated. It is our hypothesis that such clinical phenotyping can lead to better patient stratification for therapy.

In the present study, we determined the phenotype of a cohort of men with documented CPPS using the UPOINT system and assessed the frequency of individual domains and their effect on symptom severity.

MATERIAL AND METHODS

We reviewed the clinical records of 90 new patients with a diagnosis of CPPS seen at the Cleveland Clinic by 1 physician (D.A.S.) and whose information had been recorded in an institutional review board-approved database. Each patient had had their symptom severity measured using the National Institutes of Health Chronic Prostatitis Symptom Index (CPSI),[4] reported as subscores for pain, urinary, and quality of life, as well as the total score. A review of the history, physical examination findings, and urine and expressed prostatic secretions or postmassage urine culture results led to a yes/no classification for each of the 6 UPOINT domains (Table 1). Although all patients had had cultures performed and had undergone postvoid bladder ultrasonography and palpation of the pelvic floor muscles, not all patients were specifically questioned about depression or symptoms of catastrophizing (helplessness, hopelessness), which could have resulted in an underestimation of positive results for the psychosocial dysfunction domain. Nevertheless, questions regarding depression were a part of the review of systems, and many patients volunteered information on helplessness and hopelessness. The patients were a mixture of newly diagnosed, relatively treatment naive (although all had previously received some therapy, usually antibiotics) and tertiary referral patients in whom multiple previous therapies had failed.

As in previous studies, the CPSI score appeared normally distributed; therefore, parametric statistics were used. Analysis of variance was used for comparison between multiple groups, and Bonferroni's multiple comparison test was then used to compare pairs of groups. For comparison of categorical data, the nonparametric Kruskall-Wallis test was used. The unpaired Student t test was used for comparison between scores in patients positive or negative for each domain. Significance was set at $P < .05$; no a priori power calculation could be done because, as the first analysis of this kind, we could not know the range or variance of results.

RESULTS

The mean patient age in this cohort was 44.3 years (range 21-71), with a median duration of symptoms of 30 months (range 3-444). The patients had CPSI scores typical of those reported by us in previous clinical studies: pain 10.8 ± 3.8 (range 0-20), urinary 4.4 ± 3.1 (range 0-10), quality of life 8.5 ± 2.6 (range 2-12), and total 23.7 ± 7.3 (range 6-42). The number of patients with positive findings for each domain was 47 (52%), 31 (34%), 55 (61%), 14 (16%), 33 (37%), and 48 (53%) for the urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness domains, respectively. The total number of positive domains ranged from 1 (22%) to 6 (only 1 patient had all 6, and 6 patients had positive findings for 5 domains; Fig. 1). A stepwise increase was found in the total CPSI score as the number of positive domains increased from a mean of 18.1 ± 1.2 for patients with 1 positive domain to 31.7 ± 2.3 for those with 5 or 6 positive domains ($P < .0001$, analysis of variance). Stratifying patient by the total CPSI score as having mild (0-15), moderate (16-29), or severe (>29) symptoms revealed that, as the symptom severity increased, so did the number of positive domains (mild 1.73 ± 0.14, moderate 2.28 ± 0.15, and severe 3.59 ± 0.25; $P < .0001$, analysis of variance or Kruskall-Wallis test). Although patient age of less than or greater than the mean of 45 years did not influence the number of positive domains, a symptom duration of >2 years was associated with a significantly greater number of positive domains (2.93 ± 0.21 vs 2.26 ± 0.14, $P = .01$).

When the total CPSI score was compared for the presence of each domain, significantly increased symptoms were seen in patients positive for the urinary, psy-

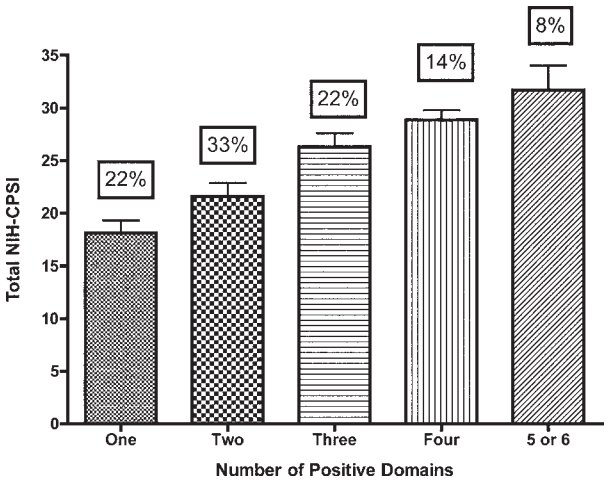

Figure 1. Mean total symptom score by number of urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness (UPOINT) domains. Incidence of each domain number given in box above each column. Significant difference seen in total chronic prostatitis symptom index score between groups ($P < .0001$, analysis of variance).

chosocial, organ specific and neurologic/systemic domains (Fig. 2). When this analysis was repeated for the pain subscore (Fig. 3), the presence of positivity for the psychosocial, neurologic/systemic, and tenderness domains was associated with significantly greater CPSI scores. The urinary subscores were only influenced by the urinary (no 2.0 ± 0.29 vs yes 6.5 ± 0.31; $P < .0001$) and organ-specific (no 3.6 ± 0.53 vs yes 4.9 ± 0.39; $P = .049$) domains; however, the definition of these domains predicted this linkage because they include both urinary components. The only domains associated with significantly increased quality-of-life subscores were the psychosocial (no 8.0 ± 0.34 vs yes 9.5 ± 0.38, $P = .007$) and neurologic/systemic (no 7.9 ± 0.35 vs yes 9.6 ± 0.34; $P = .001$) domains.

COMMENT

Patients with urologic chronic pelvic pain syndromes, including CPPS and interstitial cystitis, are a heterogeneous mix that share clinical features defined by their syndromes but have diverse etiologies and different responses to therapies. Currently, no biomarkers have been validated to help guide classification and treatment. In response to this, we have proposed a clinical phenotype classification in an attempt to better stratify patients with urologic CPPS according to the likely etiologic mechanisms and to help guide therapy.[3] Each domain has been defined by clinical parameters and each is associated with evidence-based treatments. If this classification is to be relevant and useful, a diversity of phenotypes should be present in a typical patient population and some correlation with symptom severity should be present.

In the present study, we applied the UPOINT phenotype domains retrospectively to a population of men diagnosed with CPPS at a tertiary referral center. The patients were a mix of patients with early-onset and long-term treatment-recalcitrant disease. Suitable documentation of the clinical features was present for all the domains as a part of our routine care, with the exception that depression and catastrophizing were not always specifically questioned. Thus, the incidence of patients with psychosocial-positive findings might have been underestimated. Nevertheless, the patients were typically forthcoming with how helpless, hopeless, and depressed they felt, and more than one third had findings positive for this domain.

The first key observation was that the patients did show a diversity of phenotype patterns, for both individual domains and the number of positive domains, and every patient could be successfully classified. All domains had at least one third of the patients in each yes/no category, except for Infection at 16%. This number was greater than the 7% found in the Chronic Prostatitis Cohort study[5]; however, our patients did include more antibiotic-naive or undertreated patients than did that National Institutes of Health cohort. It should be emphasized that patients with true category II chronic bacterial prostatitis (recurrent urinary tract infection with bacteria recovered from the prostate between symptomatic episodes) were excluded from phenotyping in our population. Most patients had 1-3 positive domains, but 22% did have ≥4. The symptom duration correlated directly with the number of positive domain, in keeping with the hypothesis that ongoing local tissue injury and inflammation can lead to local muscle spasm, central and peripheral neurologic changes (allodynia, hyperalgesia), and psychosocial changes that can maintain the clinical syndrome years after the initiating injury has resolved.[6]

The second key observation was that symptom severity, as measured by the National Institutes of Health CPSI correlated directly with the number of positive domains. A stepwise increase was found in the CPSI score as the number of positive domains increased for the total CPSI score, pain subscore, and urinary subscore. A threshold effect was found for the quality-of-life subscore, with an increase once 3 domains were positive. We did not necessarily expect this finding, because acute pain within the genitourinary tract can be excruciating without any systemic or other mitigating factors (eg, acute renal colic). With chronic pain, however, the reported severity and quality of life effect can be related to psychological stress and catastrophizing,[7] and central sensitization can lead to an increased perception of pain (hyperalgesia and allodynia).[8] Increased pain severity with more positive domains supports the multifactorial nature of CPPS, as well as the need for multimodal therapy for optimal resolution of the symptoms.

Classifying patients according to the clinical phenotype will allow for exploration of the relative contribution of each domain to the severity of symptoms and, ultimately, to the treatment response. In respect to the total CPSI score, the domains that were associated with

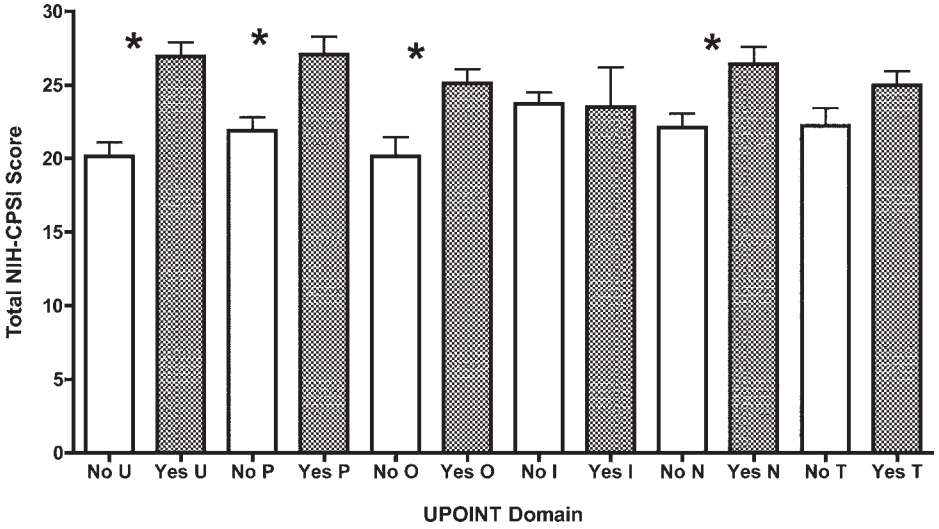

Figure 2. Comparison of mean total symptom score in patients with or without each urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness (UPOINT) domain. *$P < .05$.

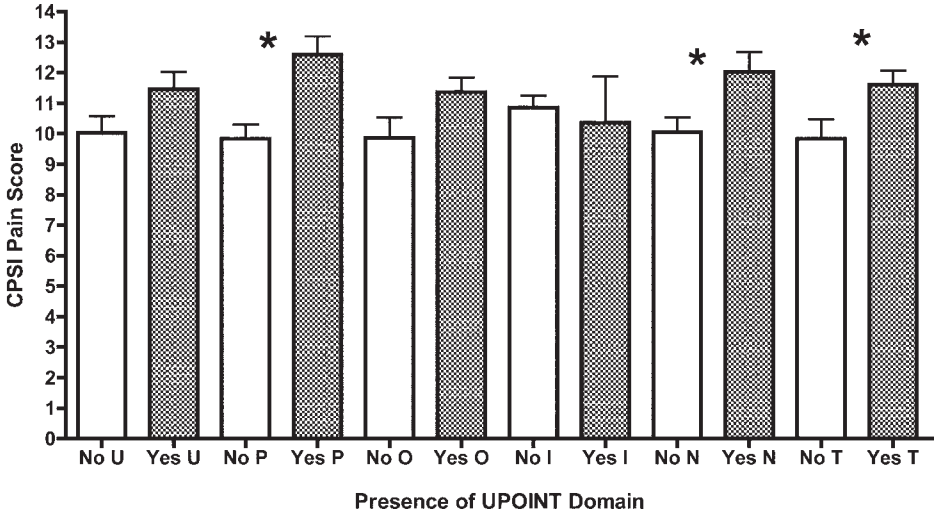

Figure 3. Comparison of mean pain symptom subscore in patients with or without each urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness (UPOINT) domain. *$P < .05$.

significantly greater scores were the urinary, psychosocial, neurologic, and organ-specific domains. The definition of the urinary domain did include a greater urinary subscore, a confounding factor. Because pain is the primary symptom in CPPS[9] and the principal driver of treatment response,[10] we studied the effect of positive domains on the CPSI pain subscore. Significant pain score increases were seen with positive findings for the psychosocial, neurologic, and tenderness of pelvic muscle domains. This re-enforces the multiplier effect that extraprostatic factors have on the generation and magnification of pain perception in patients with CPPS and suggests that therapy that does not address these domains could be ineffective.

It appears, therefore, that the UPOINT classification, when applied to men with CPPS, yields phenotypes that show a heterogeneity for individual domains and the number of positive domains. A correlation was found between the number of positive domains and symptom severity. The domains that are extraprostatic in etiology (ie, psychosocial, neurrologic/systemic, and tenderness) have a significant effect on pain perception. Because each domain is associated with specific effective therapies, we would hypothesize that multimodal therapy selected on the basis of the UPOINT phenotype would have the greatest chance for success. For instance, a patient positive only for the urinary and infection domains might benefit most from an antibiotic[11] and α-blocker.[12] A patient positive only for the psychosocial, organ-specific, neurologic/systemic, and tenderness domains might benefit most from cognitive behavioral therapy,[13] quercetin,[14] pregabalin,[15] and pelvic floor physical therapy.[16] This hypothesis is the subject of a prospective study. With larger numbers from this prospective study, we would hope to perform multivariate analyses to explore more fully the interaction among the domains, symp-

toms, and outcome. Finally, as new biomarkers and therapies are validated, they can be incorporated into this classification system. Thus, the population of patients subjected to each therapy can be enriched with those most likely to benefit, a classic application of Bayesian theory,[17] ideal for complex conditions requiring multimodal therapy.

References

1. Shoskes DA, Hakim L, Ghoniem G, et al. Long-term results of multimodal therapy for chronic prostatitis/chronic pelvic pain syndrome. *J Urol.* 2003;169:1406-1410.
2. Nickel JC, Ardern D, Downey J. Cytologic evaluation of urine is important in evaluation of chronic prostatitis. *Urology.* 2002;60: 225-227.
3. Shoskes DA, Nickel JC, Rackley RR, et al. Clinical phenotyping in chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: a management strategy for urologic chronic pelvic pain syndromes. *Prostate Cancer Prostate Dis*. Epub 2008 July 22.
4. Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. *J Urol.* 1999;162:369-375.
5. Schaeffer AJ, Knauss JS, Landis JR, et al. Leukocyte and bacterial counts do not correlate with severity of symptoms in men with chronic prostatitis: the National Institutes of Health Chronic Prostatitis cohort study. *J Urol.* 2002;168:1048-1053.
6. Pontari MA, Ruggieri MR. Mechanisms in prostatitis/chronic pelvic pain syndrome. *J Urol.* 2008;179:S61-S67.
7. Tripp DA, Nickel JC, Wang Y, et al. Catastrophizing and pain-contingent rest predict patient adjustment in men with chronic prostatitis/chronic pelvic pain syndrome. *J Pain*. 2006; 7:697-708.
8. Meeus M, Nijs J. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol.* 2007;26:465-473.
9. Krieger JN, Egan KJ, Ross SO, et al. Chronic pelvic pains represent the most prominent urogenital symptoms of "chronic prostatitis." *Urology*. 1996;48:715-721.
10. Propert KJ, Litwin MS, Wang Y, et al. Responsiveness of the National Institutes of Health chronic prostatitis symptom index (NIH-CPSI). *Qual Life Res*. 2006;15:299-305.
11. Nickel JC, Xiang J. Clinical significance of nontraditional bacterial uropathogens in the management of chronic prostatitis. *J Urol.* 2008;179:1391-1395.
12. Cheah PY, Liong ML, Yuen KH, et al. Terazosin therapy for chronic prostatitis/chronic pelvic pain syndrome: a randomized, placebo controlled trial. *J Urol.* 2003;169:592-596.
13. Nickel JC, Mullins C, Tripp DA. Development of an evidence-based cognitive behavioral treatment program for men with chronic prostatitis/chronic pelvic pain syndrome. *World J Urol.* 2008;26:167-172.
14. Shoskes DA. Phytotherapy in chronic prostatitis. *Urology*. 2002;60: 35-37.
15. Vranken JH, Dijkgraaf MG, Kruis MR, et al. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain*. 2008;136:150-157.
16. Anderson RU, Wise D, Sawyer T, et al. Integration of myofascial trigger point release and paradoxical relaxation training treatment of chronic pelvic pain in men. *J Urol.* 2005;174:155-160.
17. Kadane JB. Bayesian methods for health-related decision making. *Stat Med.* 2005;24:563-567.

EDITORIAL COMMENT

This study presents a framework from which to treat the individual patient with chronic pelvic pain syndrome (CPPS) and to study multimodal therapy for CPPS. This framework is relatively new from a CPPS research perspective, because practically all large studies of treatment have been single-agent randomized controlled trials. The findings from these randomized controlled trials have been conflicting, but the large studies have shown most agents to be ineffective. From a clinical viewpoint, the idea of treating the individual patient with chronic disease in a holistic fashion according to particular symptoms that includes multiple organ systems and the psychosocial context is well established. In subspecialty practice, however, it can be infrequently or haphazardly applied. It remains to be seen whether most urologists can adapt themselves from the mindset applicable to the treatment of acute disease and surgical cancer to the mindset of treating chronic conditions. The urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness (UPOINT) system requires a much broader focus than that for organ-based treatment. Patients also need to be guided into the attitudes required for managing chronic conditions with multisystem manifestations and to not expect the "magic bullet" cure.

Using this paradigm in research practice will be challenging, because subset analysis will require large cohorts of patients and placebo controls difficult to obtain. Furthermore, each domain could still be heterogeneous in etiology and produce uneven treatment results. If such research is done, novel approaches could be required to determine meaningful and generalizeable outcomes. The sequential therapy, single-patient randomized trials or approaches used in multiagent chemotherapy regimens might be applicable.

From a clinical viewpoint, I believe patients with CPPS might benefit from this more holistic approach to care. Chronic disease, and chronic pain, in particular, affect many aspects of patients' lives. Addressable psychosocial problems can either precede or follow the onset of CPPS. Hypersensitivity and other local and systemic symptoms can also precede or result from CPPS. Using the UPOINT approach or a modification will require that the urologist look beyond the urinary system and treat the whole patient. It might require multispecialty consultation, with the urologist orchestrating the care. The urologist will need to consider the whole patient and try to find aspects of the syndrome that are amenable to treatment. Musculoskeletal tenderness might require exercise and physical therapy, depression or catastrophizing might require psychotropic medications or counseling, and chronic pain might require long-term management. The treatment of one system could have benefits in the other systems.

The ultimate utility of this approach will need to be determined by research, but I am guessing the patient will feel well cared for if it is used.

Richard E. Berger, M.D., Department of Urology, University of Washington, Seattle, Washington

doi:10.1016/j.urology.2008.10.034