Lower Urinary Tract Symptoms and Efficacy of Anticholinergic Drugs in Patients Remaining Disease-Free After Radical Retropubic Prostatectomy.

Seung Woo Yang,[1] Yong Gil Na,[1] Ki Hak Song,[1] Ju Hyun Shin,[1] Young Seop Chang,[2] Jong Mok Park,[1] Chung Lyul Lee,[1] Jae Sung Lim[1]*

Purpose: This study was conducted to evaluate lower urinary tract symptoms (LUTS) change in patients with localized prostate cancer after radical retropubic prostatectomy (RRP) and examine the efficacy of anticholinergic drugs to treat patients suffering from storage symptoms.

Materials and Methods: Among 50 patients who underwent RRP for prostate cancer, 40 who did not undergo additional treatment that might affect their urination pattern were included in the analysis. The International Prostate Symptom Score (IPSS), quality of life (QoL) score, and uroflowmetry were analyzed prior to RRP and 12 months after RRP. Twelve months after RRP, patients desiring improvement of storage symptoms were administered anticholinergic drugs for 6 months; the effects of such treatments were analyzed 3 and 6 months later.

Results: Preoperatively and at 12 months after surgery, the mean IPSS for patients were 10.9 ± 6.7 and 9.2 ± 5.7, respectively. The mean IPSS for patients desiring improvement of storage symptoms before and after administration of medication were 9.7 ± 5.9 and 9.0 ± 4.4, respectively. In particular, the mean storage symptom composites improved significantly after administration of medication. There were no statistically significant differences in frequency between baseline and 3-month, but frequency was improved significantly after 6 months. Urgency and nocturia were improved significantly after 3 months.

Conclusion: In patients undergoing RRP, urinary symptoms change over time, with worsening storage symptoms. Our results suggest that, in patients who had discomfort with storage symptoms after RRP, anticholinergic drugs significantly improved symptoms and QoL.

Keywords: lower urinary tract symptoms/etiology; prospective studies; prostatectomy/methods; postoperative complications; prostatic neoplasms/surgery; quality of life; urination disorders/drug therapy.

INTRODUCTION

Prostate cancer is the second most common cause of cancer-related deaths and the most common malignancy diagnosed in the United States.[1] There are many treatment options for early stage prostate cancer including watchful waiting, radical prostatectomy, radiotherapy, and hormonal therapy depending upon each patient's performance status, demands, and the doctor – patient relationship. Despite many years of treating prostate cancer, there is no gold standard in terms of efficacy. However, radical prostatectomy is most frequently used to treat localized prostate cancer because this technique can lead to complete removal of cancer cells.[2] Indeed radical prostatectomy can lead to secondary effects, such as sphincter dysfunction, that require clinical management. Radical prostatectomy removes the prostate and divides the trigone and posterior urethra, thereby inducing denervation and ischemic change.[3] It is well known that storage and voiding symptoms are common in men with prostate cancer who undergo radical prostatectomy, significantly affecting their quality of life (QoL).[4] Because many of these patients have bladder outlet obstruction (BOO) and detrusor overactivity before treatment, it is important to understand the impact of radical prostatectomy on lower urinary tract symptoms (LUTS) and urinary incontinence.[5] According to the European Association of Urology guidelines, a trial of antimuscarinic drugs is the appropriate medical approach for post-radical prostatectomy patients with mixed urinary incontinence symptoms and/or urgency.[6] Because of increasing awareness of health and QoL for patients with LUTS, the patient-reported health-related QoL has become an important barometer when evaluating the effect of treatment for people who suffer

[1] Department of Urology, Chungnam National University School of Medicine, Daejeon, Korea.
[2] Department of Urology, Konyang University College of Medicine, Daejeon, Korea.
*Correspondence: Department of Urology, Chungnam National University Hospital, 282 Monwha-ro, Jung-gu, Daejeon 35015, Korea.
Tel: +82 42 2807779. Fax: +82 42 2570966. E-mail: uro17@cnu.ac.kr.
Received November 2015 & Accepted March 2016

from urinary symptoms.[7] Here, we present the results of a longitudinal study to clarify the effect of radical retropubic prostatectomy (RRP) on LUTS, except pure stress urinary incontinence. The aim of this study was to evaluate changes in LUTS and the efficacy of anticholinergic drugs in patients remaining disease-free after RRP.

MATERIALS AND METHODS

Medical records were collected prospectively for all patients who underwent RRP in our hospital between January 2009 and January 2012 (mean age 66.5 years, mean prostate specific antigen [PSA] 12.3 ng/mL). This study was approved by the Chungnam National University Hospital institutional review board (IRB No. CNUH 1007-86), and all participants signed informed consent forms. All patients were suspected of having prostate cancer based on positive results from digital rectal examinations, serum PSA, and transrectal ultrasonography (TRUS). All patients underwent TRUS-guided prostate biopsy, and prostate cancer was confirmed by pathology after RRP. All patients were < 75 years old and had serum PSA < 50 ng/mL. We included patients who agreed not to seek or use any other form of treatment for bladder dysfunction during the study. Exclusion criteria included prior treatment with radiation therapy, concomitant use of medications with antiandrogenic activity, prior history of cancer, biochemical recurrence, or severe renal or hepatic impairment. We also excluded patients with active or recurrent urinary tract infections, uncontrolled diabetes, or pure stress urinary incontinence. Fifty patients were initially enrolled in the study; however, 10 had undergone adjuvant or salvage radio- and/or hormonal therapy during or up to 12 months after RRP, and were therefore excluded from the study since such additional therapies may impact LUTS. A total of 40 patients were enrolled in the study. LUTS was assessed based on the International Prostate Symptom Score (IPSS) and the IPSS QoL score, which are both validated.[8] The IPSS is a self-administered seven-item questionnaire surveying incomplete emptying, intermittency, weak stream, and straining (voiding symptom composites), and frequency, urgency, and nocturia (storage symptom composites). Each question is scored separately from 0 to 5, with a higher score representing a worse outcome. The IPSS ranges from 0 to 35, with scores of 0, 1 to 7, 8 to 19, and 20 to 35 indicating absent, mild, moderate, and severe symptoms, respectively. The IPSS QoL score quantifies the QoL for specific LUTS, and is scored from 0 to 6, with a higher score indicating worse health.

Table 1. Clinical characteristics of the patients (n = 40).

Characteristics	Values
Mean age (years)	66.5 ± 5.8
Age (years)	
< 60	6 (15)
60~69	18 (45)
≥ 70 16 (40)	
Mean PSA at diagnosis (ng/mL)	12.3 ± 8.5
PSA at diagnosis (ng/mL)	
< 4	2 (5)
4~10	18 (45)
> 10	20 (50)
Gleason score	
≤ 6	19 (47.5)
7	14 (35)
≥ 8	7 (17.5)
Clinical tumor classification	
T1	24 (60)
T2	16 (40)
Prostate volume (mL)	
< 20	4 (10)
20 - 40	32 (80)
> 40	4 (10)

Abbreviation: PSA, prostate-specific antigen.
Values are presented as mean ± standard deviation and number (percentage).

The urinary flow rates (only voids > 150 mL were included) and IPSS were recorded before and at each visit 12 months after RRP. Residual urine was determined by transabdominal ultrasonography. Out of 40 patients, 34 who desired further improvement of storage symptoms were medicated by anticholinergic drugs (solifenacin 5 mg, once daily) for 6 months. The urinary flow rates, IPSS, QoL, the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF),[9] and the King's Health Questionnaire (KHQ)[10] were recorded at 3 and 6 months after administration of medication. The ICIQ-SF and KHQ were self-completed by the patients. The ICIQ-SF assesses and scores frequency of urine loss (0–5), severity (0–6), and urine leakage interfering with daily life (0–10), and also includes an unscored self-diagnostic question. The scores are added (score range from 0 to 21), with a higher score indicating a worse QoL. The KHQ is a measure of health-related QoL that includes two single-item domains (general health perception and incontinence impact), seven multi-item domains (role limitations, physical limita-

Table 2. Comparison of uroflowmetry and International Prostate Symptom Score prior to and 12 months after surgery (n = 40).

Variables	Before RRP	After RRP	*P* Value
Maximal flow rate (mL/sec)	17.9 ± 5.3	18.6 ± 6.4	.162
Residual urine (mL)	31 ± 29.5	27 ± 19.1	.160
Total IPSS	10.9 ± 6.7	9.2 ± 5.7	.075
Voiding	6.7 ± 4.5	4.4 ± 3.6 b	.003
Storage	4.2 ± 2.9	4.8 ± 2.8	.136
Incomplete emptying	1.4 ± 1.4	0.8 ± 1.0 a	.010
Frequency	1.7 ± 1.2	1.6 ± 1.0	.618
Intermittency	1.8 ± 1.5	1.2 ± 1.2 a	.033
Urgency	0.9 ± 1.2	1.5 ± 1.5 a	.027
Weak stream	2.3 ± 1.5	1.4 ± 1.1 b	.005
Straining	1.3 ± 1.5	1.0 ± 1.1	.208
Nocturia	1.6 ± 1.3	1.7 ± 1.2	.570
Quality of life	2.0 ± 1.3	2.5 ± 1.1 a	.020

Abbreviations: IPSS, international prostate symptom score; RRP, radical retropubic prostatectomy.
Values are presented as mean ± standard deviation.
a $P < .05$, b $P < .01$ versus before RRP.

tions, social limitations, personal relationships, emotional problems, and sleep/energy disturbances), and a multi-item severity measure.[9] The two single item domains and the seven multi-item domains of the KHQ are scored on a scale from 0 (best) to 100 (worst). Reported adverse events during the treatment period were also analyzed.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 18.0. Parametric numeric data were analyzed with the paired *t*-test and nonparametric data were assessed using the Wilcoxon's signed rank test. Values are expressed as the mean ± standard deviation

Table 3. Comparison of uroflowmetry and International Prostate Symptom Score prior to administration of medication, and 3 and 6 months after medication (n = 34).

Variables	Baseline	3-Month	6-Month	*P* Value a	*P* Value b
Maximal flow rate (mL/sec)	18.7 ± 6.7	18.5 ± 6.4	18.1 ± 4.8	.661	.439
Residual urine (mL)	26.8 ± 20.2	28.8 ± 17.9	28.5 ± 17.4	.256	.439
Total IPSS	9.7 ± 5.9	9.3 ± 5.3	9.0 ± 4.4 c	.082	.026
Voiding	4.6 ± 3.6	4.7 ± 3.4	4.8 ± 2.8	.292	.353
Storage	5.2 ± 2.9	4.6 ± 2.4 d	4.2 ± 2.1 d	.001	.001
Incomplete emptying	0.8 ± 1.0	0.8 ± 0.9	0.9 ± 0.7	.325	.254
Frequency	1.7 ± 1.1	1.6 ± 1.0	1.4 ± 0.8 c	.160	.027
Intermittency	1.2 ± 1.2	1.2 ± 1.2	1.3 ± 0.9	.571	.414
Urgency	1.7 ± 1.5	1.4 ± 1.2 d	1.4 ± 1.1 d	.006	.008
Weak stream	1.5 ± 1.1	1.5 ± 0.9	1.4 ± 0.9	.661	.254
Straining	1.1 ± 1.1	1.1 ± 1.1	1.2 ± 1.1	.160	.096
Nocturia	1.7 ± 1.2	1.5 ± 1.0 c	1.4 ± 1.0 d	.017	.003
Quality of life	2.6 ± 1.2	2.6 ± 1.1	2.3 ± 1.0 c	.325	.016

Abbreviation: IPSS, international prostate symptom score.
Values are presented as mean ± standard deviation.
a Compares values between the baseline and 3 months of therapy; b Compares values between the baseline and 6 months of therapy; c $P < .05$ versus baseline; d $P < .01$ versus baseline.

Table 4. Comparison of questionnaire scores prior to, and 3 and 6months after medication (n = 34).

Variables	Baseline	3-Month	6-Month	*P* Value a	*P* Value b
ICIQ-SF score	4.9 ± 1.8	4.8 ± 1.4	4.6 ± 1.4	.404	.154
KHQ score	25.6 ± 7.1	24.8 ± 6.2	23.5 ± 6.6 c	.263	.019

Abbreviations: ICIQ-SF, International Consultation on Incontinence Questionnaire-Short Form; KHQ, King's Health Questionnaire.
Values are presented as mean ± standard deviation.
a Compares values between the baseline and 3 months of therapy; b Compares values between the baseline and 6 months of therapy; c $P < .05$ versus baseline.

(SD), with $P < .05$ considered significant.

RESULTS

Characteristics of the 40 patients at the time of diagnosis are presented in **Table 1**. At diagnosis the mean PSA value was 12.3 ng/mL (range 3.2 – 43.6 ng/mL) and the median prostate volume was 28.6 cm^3 (range 16 – 56 cm^3). The overall mean total IPSS, which was 10.9 ± 6.7 before RPP, decreased over time after RPP to 9.2 ± 5.7 at 12 months after surgery, a difference that did not reach the level of significance. The overall mean IPSS QoL score increased with time after RPP, and the difference reached the level of significance at 12 months after RRP, while the change in IPSS did not. Individual analysis of each question reflected in the IPSS demonstrated that the symptoms of incomplete emptying, intermittency, and weak stream were significantly relieved after surgery, while the symptom of urgency significantly worsened after RRP (**Table 2**). The overall mean total IPSS in the patient population seeking medication to relieve LUTS, which was 9.7 ± 5.9 before medication, was reduced significantly to 9.0 ± 4.4 at 6 months after medication. The overall mean IPSS QoL score decreased with time after medication in parallel with the IPSS, and the difference from baseline reached the level of significance at 6 months after medication. No significant change was noted in any of the four voiding symptom composites. However, all three of the storage symptom composites decreased significantly at 6 months after medication. The results of the uroflow test before and after medication showed that maximal uroflow changed from 18.7 ± 6.7 mL/sec to 18.1 ± 4.8 mL/sec, and residual urine changed from 26.8 ± 20.2 mL to 28.5 ± 17.4 mL, neither of which reached the level of significance (**Table 3**). The ICIQ-SF score improved from 4.9 ± 1.8 to 4.6 ± 1.4 at 6 months after medication, which did not reach the level of significance. The KHQ score significantly improved from 25.6 ± 7.1 to 23.5 ± 6.6 at 6 months after medication (**Table 4**). The overall incidence of adverse events was 35.3% (12/34 patients), and all were mild in intensity. No patients experienced severe hepatic dysfunction, renal failure, or cardiovascular effects. Dry mouth was the most frequently reported adverse event (23.5% or 8/34), followed by constipation in 14.7% (5/34). No patients discontinued treatment due to adverse events (**Table 5**).

DISCUSSION

Prostate cancer is likely to remain one of the most important issues in men's health for the foreseeable future. Opinions differ regarding the optimal management of prostate cancer. In men > 70 years of age, or in those with appreciable co-morbidity, a conservative management approach is generally accepted. However, healthy younger men are more likely to live long enough to experience disease progression; therefore, radical prostatectomy and radiotherapy, as well as "watchful waiting", are options in this group. Use of radical prostatectomy has been increasing in patients with early stage disease, and is indicated for men with a life expectancy of > 10 years.[11] The first surgical management of prostate cancer was performed by Millin and colleagues in 1947.[12] Since then, several improved operative methods have been established. Surgical management of the dorsal vein complex and a procedure effective for preserving the neurovascular bundle were described by Walsh and colleagues[13] Consequently, the incidence of postoperative complications has been decreasing. However, postoperative LUTS continue to occur at a constant rate and negatively affect the QoL of the patients. Thus, QoL issues need to be considered when deciding on the best treatment option. Relief of obstruction by radical prostatectomy has been reported by several investigators to diminish LUTS. Schwartz and colleagues indicated, in patients with moderated or high degree symptoms, that radical prostatectomy significantly reduces the total IPSS and positively affects LUTS.[14] Our investigation further extended knowledge of the impact of RRP on LUTS, demonstrating that RRP provides major benefits for men with LUTS. Namiki and colleagues reported that storage symptoms, such as frequency and nocturia, do not improve after radical prostatectomy, or are exacerbated in some cases.[15] Results from the present study were similar, in that overall urinary symptoms significantly improved after operation, yet patients' QoL progressively worsened. Specifically, progressively

Table 5. Adverse events due to anticholinergic drugs (n = 34).

Adverse Events	3-Month	6-Month
Dry mouth	6 (17.6)	8 (23.5)
Constipation	3 (8.8)	5 (14.7)
Blurred vision	0 (0)	1 (2.9)
Headache	2 (5.9)	1 (2.9)
Dizziness	1 (2.9)	1 (2.9)

Values are presented as number (percentage).

deteriorating storage symptom composites negated the improvements in voiding symptom composites, resulting in worsened QoL. This information is important when counseling patients about treatment options for localized prostate cancer.

The improvement of LUTS is probably mostly attributable to obstruction relief by RRP. It is well known that benign prostatic hypertrophy can cause BOO, secondary bladder overactivity, and reduction in functional bladder capacity, which may result in storage symptoms.[16] Conversely, these symptoms can be reversed with obstruction relief by prostatectomy.[17] Several investigators have also reported IPSS improvement concurrent with an increase in urinary flow rate after RRP in patients with moderate to severe LUTS.[18] Although our study lacked urodynamic data, these findings suggest an association between BOO relief by RPP and IPSS improvement. RRP increased urgency and nocturia (not significantly) in our study. In contrast, Namiki and colleagues[19] reported that nocturia did not return to the baseline level within 2 years after surgery. Gomha and colleagues[20] reported that, following radical prostatectomy, a substantial proportion of patients were affected by detrusor overactivity, impaired detrusor contractility, decreased compliance, and sphincter weakness. Bladder denervation during surgery has been suggested as one reason for these abnormalities. Wide anatomical dissection around the prostate and bladder neck may disrupt regional afferent and efferent innervation, causing outlet lethargy and partial denervation of the detrusor muscle.[21] Also, Jung and colleagues[22] demonstrated that leakage of urine into the proximal urethra could increase bladder activity by stimulating urethral afferents, which in turn modulate the micturition reflex and induce detrusor instability. Thus, bladder denervation during surgery and postoperative urine incontinence may be implicated in the deterioration of storage symptoms, even though recovery from urinary incontinence after RPP is considerable. For patients with LUTS, these adverse effects may exacerbate urgency or nocturia. The reversal of detrusor overactivity by relief of BOO might have been dampened by adverse effects such as bladder denervation or subtle urine leakage. In patients with preoperative LUTS, communicating that voiding symptoms can be improved after radical prostatectomy will be important to promoting QoL. In our study, bladder storage symptoms aggravated after prostatectomy. We believe that an irritated urethra caused by urine leakage due to nerve or sphincter injury during prostatectomy caused decreased bladder compliance and detrusor overactivity. Also, extensive incisions during prostatectomy can damage the efferent and afferent nerves of the bladder trigone, bladder neck, and detrusor muscle. Therefore, storage symptoms may be aggravated as opposed to voiding symptoms after prostatectomy.[22] In general, storage symptoms are managed with anticholinergic drugs, since detrusor contractions are mediated by cholinergic receptor stimulation. The results of the current study show that anticholinergic drugs act not only on detrusor muscle but also on muscarinic receptors located on bladder afferent nerve terminals and on urothelium.[23] Recent pharmacologic advancements have produced anticholinergic drugs with an increased duration of action and fewer side effects, such as dry mouth and constipation. In our study, taking anticholinergic drugs significantly improved storage symptoms after radical prostatectomy. Our findings supplement subjective questionnaire-based reports of decreased urgency and frequency reported in trials of solifenacin.[24,25] Our study will help clarify treatment options for patients with localized prostate cancer who consider refusing prostatectomy due to not wanting changes in LUTS.

Limitations of our study are its small sample size and short follow-up period after medication, which allows for potential selection bias. Long-term follow-up data on this patient population is needed. To clarify the mechanism of LUTS improvement, further investigation including urodynamic studies and overactive bladder symptoms score, will be needed. Further large prospective studies and long-term follow-up will be required to fully evaluate the drug efficacy results.

CONCLUSIONS

Postoperative LUTS is a common adverse effect of RRP, potentially leading to a significantly diminished QoL. However, the exact cause of postoperative LUTS was not determined. Although our study was relatively small, it provides important and detailed information about the impact of RRP on LUTS and LUTS-related QoL. It also supports the benefits of anticholinergic drugs as treatment for postoperative LUTS. We hope

that our findings will assist patients, families, and doctors in their discussions about treatment expectations and outcomes.

ACKOWLEDGEMENTS

This work was supported by Chungnam, National University Hospital Research Fund, 2011.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics, 2014. CA Cancer J Clin. 2014;64:9-29.
2. Jani AB, Hellman S. Early prostate cancer: clinical decision-making. Lancet. 2003;361:1045-53.
3. Song C, Lee J, Hong JH, Choo MS, Kim CS, Ahn H. Urodynamic interpretation of changing bladder function and voiding pattern after radical prostatectomy: a long-term follow-up. BJU Int. 2010;106:681-6.
4. Hollenbeck BK, Lipp ER, Hayward RA, Montie JE, Schottenfeld D, Wei JT. Concurrent assessment of obstructive/irritative urinary symptoms and incontinence after radical prostatectomy. Urology. 2002;59:389–93.
5. Masters JG, Rice ML. Improvement in urinary symptoms after radical prostatectomy: a prospective evaluation of flow rates and symptom scores. BJU Int. 2003;91:795–7.
6. Bauer RM, Gozzi C, Hubner W, et al. Contemporary management of postprostatectomy incontinence. Eur Urol. 2011;59:985-96.
7. Babic U, Santric-Milicevic M, Terzic Z, et al. Impact of voiding and incontinence symptoms on health-related life quality in Serbian male population. Urol J. 2015;12:2196-203.
8. Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992;148:1549–57.
9. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn. 2004;23:322-30.
10. Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. Br J Obstet Gynaecol. 1997;104:1374–9.
11. Sriprasad S, Feneley MR, Thompson PM. History of prostate cancer treatment. Surg Oncol 2009;18:185-91.
12. Millin T. Retropubic prostatectomy. J Urol. 1948;59:267–80.
13. Walsh PC. Anatomic radical prostatectomy: evolution of the surgical technique. J Urol. 1998;160:2418–24.
14. Schwartz EJ, Lepor H. Radical retropubic prostatectomy reduces symptom scores and improves quality of life in men with moderate and severe lower urinary tract symptoms. J Urol. 1999;161:1185–8.
15. Namiki S, Saito S, Ishidoya S, et al. Adverse effect of radical prostatectomy on nocturia and voiding frequency symptoms. Urology. 2005;66:147–51.
16. de Nunzio C, Franco G, Rocchegiani A, Iori F, Leonardo C, Laurenti C. The evolution of detrusor overactivity after watchful waiting, medical therapy and surgery in patients with bladder outlet obstruction. J Urol. 2003;169:535–9.
17. Giannantoni A, Mearini E, Di Stasi SM, et al. Assessment of bladder and urethral sphincter function before and after radical retropubic prostatectomy. J Urol. 2004;171:1563–6.
18. Kumar V, Toussi H, Marr C, Hough C, Javle P. The benefits of radical prostatectomy beyond cancer control in symptomatic men with prostate cancer. BJU Int. 2004;93:507–9.
19. Namiki S, Ishidoya S, Saito S, et al. Natural history of voiding function after radical retropubic prostatectomy. Urology. 2006;68:142–7.
20. Gomha MA, Boone TB. Voiding patterns in patients with post-prostatectomy incontinence: urodynamic and demographic analysis. J Urol. 2003;169:1766–9.
21. Giannantoni A, Mearini E, Di Stasi SM, et al. Assessment of bladder and urethral sphincter function before and after radical retropubic prostatectomy. J Urol. 2004;171:1563–6.
22. Jung SY, Fraser MO, Ozawa H, et al. Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. J Urol. 1999;162:204–12.
23. Andersson KE, Yoshida M. Antimuscarinics and the overactive detrusor - which is the main mechanism of action? Eur Urol. 2003;43:1–5.
24. Santos JC, Telo ER. Solifenacin: scientific evidence in the treatment of overactive bladder. Arch Esp Urol. 2010; 63:197–213.
25. Vardy MD, Mitcheson HD, Samuels TA, et al. Effects of solifenacin on overactive bladder symptoms, symptom bother and other patient reported outcomes: results from VIBRANT - a double-blind, placebo-controlled trial. Int J Clin Pract. 2009;63:1702–14.