Patient-Reported Quality of Life in Men with Transurethral Resection of the Prostate Undergoing Proton Therapy for Management of Prostate Cancer

Derek T. Lee, MD; Nancy P. Mendenhall, MD; Tamara L. Smith, MD; Christopher G. Morris, MS; Romaine C. Nichols, MD; Curtis Bryant, MD; Randal H. Henderson, MD, MBA; William M. Mendenhall, MD; Joseph Costa, MD; Christopher R. Williams, MD; Zuofeng Li, DSc; Bradford S. Hoppe, MD, MPH

University of Florida Proton Therapy Institute, Jacksonville, FL

Abstract

Purpose: We report on quality of life (QOL) and early toxicity among men with prostate cancer who underwent transurethral resection of the prostate (TURP) before proton therapy.

Materials and Methods: Between 2006 and 2010, 1,289 patients were treated definitively with proton therapy for prostate cancer at our institution and enrolled on a prospective outcomes-tracking protocol. Ninety-six of the men had received a TURP before proton therapy, while 1,193 men had not. Baseline comorbidities, medications, expanded prostate index composite (EPIC) score, international prostate symptom score (IPSS), and CTCAE vs.3 toxicity assessment were collected prospectively. The Kaplan-Meier product limit method was used to estimate freedom from toxicity.

Results: Men who had TURP before proton therapy had lower baseline EPIC scores for urinary incontinence, bowel summary, and sexual summary compared with the non-TURP group, but no significant difference in urinary obstructive score was observed. After controlling for baseline scores, there was no significant difference in bowel summary or sexual summary scores between the two groups over time. There were, however, differences for urinary irritation/obstruction scores and urinary incontinence scores favoring those patients who did not have a TURP-like procedure. Toxicity assessment showed that the 2-year and 5-year rates of grade 3 genitourinary toxicity in the pretreatment TURP group were 12.3% and 17.2%, respectively.

Conclusions: Pretreatment TURP was associated with both a high incidence of physician-assessed toxicity and inferior patient-reported QOL scores both before and after proton therapy treatment. Studies investigating QOL and toxicity after specific prostate cancer therapies should stratify patients by pretreatment TURP. Longer follow-up is needed to confirm if these differences ever resolve.

Introduction

There are various approaches to the definitive management of localized prostate cancer, including surgery, brachytherapy, and external-beam radiation therapy. All of these treatments result in favorable long-term survival; therefore, quality of life (QOL) and toxicity from treatment have become important considerations during the decision-making process [1–3].

Transurethral resection of the prostate (TURP) or TURP-like procedures are a risk factor that may contribute to the treatment decision for prostate cancer. TURP is a procedure that removes portions of the prostate to relieve urinary obstructive symptoms resulting from prostate enlargement, often due to benign prostatic hyperplasia (BPH). Prior studies suggest that men with prostate cancer who undergo TURP may have a greater likelihood of urinary complications after external-beam radiotherapy than men who do not undergo TURP, with rates of grade 3 gentiourinary (GU) toxicity ranging from as low as 3% [4] to as high as 16% [5]. Despite these findings, patient-reported QOL using validated instruments such as the Expanded Prostate Cancer Index Composite (EPIC) have not been well studied in this cohort of patients.

Proton therapy is an effective therapy for localized prostate cancer because it can deliver high doses of conformal radiation while sparing adjacent structures like the bladder and rectum [6]. Early outcomes studies suggest a minimal (1.9%) rate of grade 3 genitourinary (GU) toxicity after proton therapy in a general prostate cancer population [7]. In men with enlarged prostates treated with proton therapy for prostate cancer, the risk appears to be slightly elevated with a 6.4% risk of late grade 3 GU toxicity [8]. Few data exist, however, regarding the impact of a TURP-like procedure on GU toxicity following treatment with proton therapy. The present study investigates early toxicity and patient-reported QOL outcomes following proton therapy among patients who have undergone TURP or a TURP-like procedure.

Methods and Materials

Patients

The medical records of 1,289 patients treated with proton therapy for prostate cancer at our institution between 2006 and 2010 were reviewed in accordance with an institutional review board (IRB)-approved treatment protocol and the Health Insurance Portability and Accountability Act. Patients were included in this analysis if they were treated definitively with proton therapy for prostate cancer. Patients were excluded if they had received radiotherapy as salvage therapy or if their radiotherapy included elective treatment to the pelvic lymph node regions. In total, 1,289 patients were eligible for the study.

Patients who were previously treated for urinary retentive or obstructive symptoms with TURP or a TURP-like procedure, such as transurethral microwave therapy (TUMT), transurethral needle ablation (TUNA), or any type of laser surgery on the prostate, were identified. A total of 96 patients had a TURP or TURP-like procedure prior to proton therapy and the vast majority of these patients had procedures done at outside facilities, requiring record retrieval. Of these, patients who had multiple procedures (13%; n=13) were categorized by the last procedure performed before proton therapy. Most of the patients in the cohort (64%; n=62) had a traditional TURP procedure, some patients had a laser utilized in the procedure (24%; n=23), and a minority of the patients either had a TUMT (7%; n=7) or TUNA (5%; n=5).

All patients had pretreatment work-up consisting of computed tomography (CT) of the pelvis, magnetic resonance imaging (MRI) of the pelvis, a bone scan, and an internal pathology review. Patient- and disease-specific characteristics are listed in **Table 1**.

Treatment

Our protocol for simulation, treatment planning, and delivery of treatment has previously been reported in detail [7]. Briefly, all patients underwent placement of 3 to 4 visicoil fiducials under transrectal ultrasound guidance by the urology team at our institution. Thirty minutes before simulation, patients voided and then drank 16 oz of water. Patients were simulated supine with a vacuum-locked body mold. Patients underwent CT simulation immediately followed by MRI. The CT and MRI images were fused for treatment planning. Prostate and seminal vesicle targets were contoured by the treating physicians. Normal tissues, including bladder, rectum, and bowel, were manually contoured by dosimetrists. The clinical target volume (CTV) included the prostate only for low-risk patients, and the prostate and proximal 2 cm of seminal vesicles for intermediate- and high-risk patients. The planning target volume (PTV) expansion was 6-8 mm beyond the CTV in the superior-inferior axis and 4-5 mm in the axial plane. Beam angles were selected to optimize target coverage and minimize normal-tissue exposure.

Toxicity

Toxicities were recorded for each patient and scored according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [9]. Specific attention was paid to GU toxicities. All patients had toxicity assessed and recorded prior to beginning proton therapy, weekly while undergoing proton therapy, and at 6-month intervals following completion of radiotherapy. For our toxicity analysis, the beginning of proton therapy was considered the start date.

Lee et al. (2016), *Int J Particle Ther*

519

Table 1. Patient and treatment characteristics.

Characteristic	No. of patients (%)			
	TURP Group (n=96)	Non-TURP Group (n=1193)	Total (N=1289)	P-value
Median age, yrs (range)	72 (55 to 85)	66 (40 to >89)	66 (40 to >89)	<0.0001
Tumor classification				
T1a/1b/1c	63	876	939	T1 VS T2+
T2a	16	210	226	0.096
T2b	10	70	80	
T2c/3a/3b	7	36	43	
TX	0	1	1	
Gleason score				
4-6	39	599	638	4-6 vs 7 vs 8+
7	36	450	486	0.0258
8	14	97	111	
9+	7	47	54	
Prostate-specific antigen				
<10	83	996	1079	0.38
10-20	9	163	172	
>20	4	34	38	
Risk group				
Low	31	513	544	0.0194
Intermediate	41	509	550	
High	24	171	195	
Radiation dose				
<76 Gy	1	3	4	<80 vs 80+
76-79.9 Gy	77	996	1073	0.4771
80-82 Gy	18	194	212	
Diabetes	21	148	169	0.0113
Medications				
α Blocker	24	222	246	0.1362
5-α reductase inhibitor	13	88	101	0.0467
Androgen deprivation therapy	34	185	219	<0.0001
Time from procedure to treatment				
<1 year	27	-	-	-
>1 year	69	-	-	-

Abbreviations: Gy, Gray; TURP, transurethral resection of the prostate.

Follow-Up and Observed Outcomes

Follow-up care included a medical history and physical examination at 6-month intervals following treatment. EPIC, version 2.2002 [10] questionnaires were conducted before initiating proton therapy and at 6-month intervals following proton therapy. The EPIC-26 summary and subscales were then calculated and reported using a scale of 0 to 100, with higher scores indicating better outcomes. Prostate-specific antigen (PSA) tests were performed at 3-month intervals following proton therapy. For our QOL analysis, the beginning of proton therapy was considered the start date.

Statistical Analysis

SAS and JMP software were used for all statistical computations (SAS Institute, Cary, NC). A Wilcoxon signed-rank sum test was used to determine whether there was a statistically significant increase or decrease in EPIC scores between baseline and 6 months, 1 year, 2 years, and 3 years after treatment. This same series of scores and timepoints was entered into multiple regressions to adjust the effect of pre-treatment TURP by controlling for the baseline score (continuous), risk, use of hormones, diabetes, and age (< vs > 60). Fisher's exact test was performed on select items in the EPIC questionnaire related to urinary incontinence, and urinary irritative/obstructive symptoms were dichotomized to differentiate more specific QOL outcomes over time. The Kaplan-Meier product limit function was used to estimate freedom from posttreatment grade 3 GU

Table 2. EPIC composite scores over time for TURP and non-TURP patients.

Group	Timing	Pre-tx TURP			No Pre-tx TURP			P-value	
		Median	Min	Max	Median	Min	Max	Adjusted	Unadjusted
Bowel	Baseline	95.8	54.2	100.0	100.0	33.3	100.0	0.0002	-
	6 Month	91.7	20.8	100.0	95.8	16.7	100.0	0.0181	0.1667
	1 year	87.5	16.7	100.0	91.7	4.2	100.0	0.0119	0.199
	2 year	91.7	45.8	100.0	95.8	12.5	100.0	0.1395	0.9834
	3 year	95.8	25.0	100.0	95.8	5.0	100.0	0.4171	0.8308
Sexual	Baseline	49.3	0.0	100.0	70.8	0.0	100.0	<.0001	-
	6 Month	40.2	0.0	100.0	62.5	0.0	100.0	0.0026	0.8864
	1 year	36.0	0.0	100.0	56.8	0.0	100.0	0.0003	0.4728
	2 year	26.3	0.0	100.0	54.2	0.0	100.0	0.0004	0.189
	3 year	31.8	0.0	100.0	52.7	0.0	100.0	0.01	0.3406
Urinary Incontinence	Baseline	100.0	39.5	100.0	100.0	22.8	100.0	0.0177	
	6 Month	100.0	8.3	100.0	100.0	0.0	100.0	0.0073	0.0284
	1 year	91.8	0.0	100.0	100.0	6.3	100.0	0.0002	0.0073
	2 year	91.8	8.3	100.0	100.0	0.0	100.0	0.0171	0.0322
	3 year	91.8	20.8	100.0	100.0	8.3	100.0	0.0363	0.1544
Urinary Obstruction	Baseline	90.6	50.0	100.0	87.5	25.0	100.0	0.8993	-
	6 Month	87.5	25.0	100.0	93.8	6.3	100.0	0.0012	0.0002
	1 year	87.5	0.0	100.0	87.5	18.8	100.0	0.0922	0.0281
	2 year	87.5	25.0	100.0	93.8	18.8	100.0	0.1342	0.0893
	3 year	87.5	31.3	100.0	93.8	12.5	100.0	0.4293	0.0361

Abbreviations: Max, maximum; min, minimum; TURP, transurethral resection of the prostate; tx, treatment.

toxicity. The log-rank test statistic tested whether baseline characteristics predicted for increased risk of grade 3 GU toxicity among the pretreatment TURP patients. These baseline characteristics included age, use of alpha blockers or alpha reductase inhibitors, diabetes, or androgen deprivation therapy (ADT) use. All p values less than 0.05 were considered statistically significant.

Results

Patients

The cohort of patients who had a pretreatment TURP at baseline was quite different from patients who did not have a TURP. Patients in the TURP cohort were significantly older (median age, 72 vs 66 years of age at the start of treatment), had higher-risk disease, more frequently had diabetes, more frequently used 5-alpha reductase inhibitors (5ARIs), and more frequently received ADT as part of treatment (**Table 1**).

Quality of Life

The median follow-up time for administration of the EPIC QOL for the cohort was 5.3 years (range, 0.7 to 7.7 years). QOL EPIC-26 scores at baseline, 6 months, 1 year, 2 years, and 3 years were available for 97%, 89%, 88%, 78%, and 74% of the entire patient cohort and are listed by subscale in **Table 2**. At baseline, the TURP group already had lower median bowel summary, sexual summary, and urinary incontinence subscales compared to the non-TURP group. The urinary irritation/obstruction subscale was the only score that was not different at baseline. Within the TURP cohort, time from TURP to start of proton therapy (<1 year vs >1 year) and type of TURP (TURP vs TURP-like procedure) did not impact baseline QOL scores in a statistically significant manner.

After controlling for baseline scores, there was no significant difference in bowel summary or sexual summary scores between the two groups over time. There were, however, differences for urinary irritation/obstruction scores and urinary incontinence scores favoring those patients who did not have a TURP-like procedure (Table 2).

Table 3. Outcomes for specific EPIC questions over time for the TURP and non-TURP patients.

	Baseline	6 Months	1 Year	2 Years	3 Years
Leaked urine > once a day					
No TURP	6.2%	7.9%	9.7%	11.0%	9.9%
TURP	15.8%	15.4%	22.4%	25.8%	17.2%
P value	0.0023	0.0284	0.0014	0.0012	0.0854
Urinary control described by frequent dribbling or no control					
No TURP	2.1%	2.6%	3.8%	3.4%	3.9%
TURP	2.1%	5.4%	10.5%	10.6%	4.8%
P value	0.9999	0.1782	0.0089	0.0110	0.7342
Using 1 or more pads/diapers per day					
No TURP	1.0%	2.2%	3.2%	3.7%	4.2%
TURP	8.7%	9.8%	14.0%	15.2%	15.6%
P value	<.0001	0.0006	<.0001	0.0004	0.0007
Moderate or big problem with dripping or leaking urine					
No TURP	90.0%	1.6%	3.1%	3.9%	3.3%
TURP	4.3%	4.5%	7.1%	17.2%	10.9%
P value	0.0169	0.0743	0.0570	<.0001	0.0079
Moderate or big problem with pain or burning with urination					
No TURP	0.5%	2.6%	4.5%	2.0%	1.1%
TURP	0.0%	9.0%	5.9%	3.1%	3.1%
P value	0.9999	0.0043	0.5857	0.6426	0.1907
Moderate or big problem with bleeding with urination					
No TURP	0.1%	0.5%	0.5%	1.0%	0.9%
TURP	0.0%	2.3%	3.5%	4.6%	3.1%
P value	0.9999	0.0982	0.0177	0.0394	0.1420
Moderate or big problem with weak urine or incomplete emptying					
No TURP	9.7%	6.1%	10.4%	7.9%	6.1%
TURP	11.8%	13.6%	18.8%	12.5%	12.7%
P value	0.4710	0.0121	0.0282	0.2318	0.0586
Moderate or big problem with frequent urination during the day					
No TURP	13.7%	11.1%	13.7%	11.5%	11.7%
TURP	9.7%	23.3%	19.8%	15.4%	11.1%
P value	0.3419	0.0019	0.1453	0.3236	0.9999
Moderate or big problem with overall urinary function					
No TURP	7.8%	7.5%	10.5%	9.6%	8.0%
TURP	12.0%	18.9%	22.1%	21.9%	17.2%
P value	0.1637	0.0010	0.0039	0.0048	0.0184

Abbreviations: TURP, transurethral resection of the prostate.

Specific answers to questions pertaining to urinary incontinence and obstructive symptoms from the EPIC questionnaire are illustrated in **Table 3**. In particular, at 2 years following treatment more TURP patients leaked urine more than once daily (25.8% vs 11%), had frequent dribbling or no control (10.6% vs 3.4%), and required 1 or more pads/diapers for urinary leakage (15.2% vs 3.7%). Additionally, more TURP patients had moderate or big problems with dripping or leaking urine (17.2% vs 3.9%), bleeding with urination (4.6% vs 1%), and overall urinary function (21.9% vs 9.6%).

Toxicity

A total of 17 of the 96 patients in the TURP group experienced a grade 3 GU toxicity after proton therapy. The 2-year and 5-year cumulative grade 3 GU toxicity rates were 12.3% and 17.2%, respectively [9]. Some patients experienced multiple toxicities. Six patients required another TURP after treatment. Three patients required a urethral dilation procedure, 4 patients required a temporary catheter, 4 patients required hyperbaric oxygen for hematuria, 3 patients required blood transfusions, and 2 patients required cauterization for hematuria. We evaluated whether time to TURP (<1 year vs. >1 year) or type of

Lee et al. (2016), *Int J Particle Ther*

522

TURP (TURP vs. TURP-like procedure) had any impact on toxicity rates. No significant difference in toxicity was seen for time to TURP (p=0.3134) or type of TURP (p=0.5769)

Discussion

This study investigated patient-reported QOL and early toxicity in men with TURP undergoing proton therapy for prostate cancer and found that the patients with a prior TURP-like procedure had worse patient-reported QOL outcomes prior to and following proton therapy compared with patients who did not undergo a TURP.

Although both cohorts of patients were treated with proton therapy at the same institution, there were some important differences among the patients that could have contributed to the differences we observed in several of the QOL outcomes. Importantly, the patients who underwent a TURP were older and more likely to have diabetes. Some evidence suggests that older individuals have a higher risk of bowel problems, and other studies have found that older patients with diabetes are at an increased risk of fecal incontinence compared to patients who do not have diabetes [11–13]. These characteristics could explain the baseline differences seen in bowel summary score. The reason for decreased sexual QOL scores at baseline among the patients with a prior TURP-like procedure may be multifactorial as well. In addition to advanced age, evidence suggests that decreased sexual function may be attributable to diabetes or ADT use [14, 15]. Use of 5ARIs was also more prevalent among the patients with a prior TURP-like procedure. Adverse events related to sexual dysfunction have been reported in up to 8% of patients taking 5ARIs [16].

Urinary irritation/obstruction was the only subscale that was not lower at baseline in the patients with a TURP-like procedure, likely because the TURP-like procedure improved this specific area of urinary function. However, there were significantly worse urinary irritation/obstruction symptoms following treatment for the TURP group compared with the non-TURP group. This difference is likely due to the higher risk of urethral stricture for TURP patients undergoing radiation, which could cause these types of symptoms. The difference seen in urinary incontinence score at baseline is probably also attributable to the actual TURP procedure, which carries the risk of urinary incontinence [17]. Additional factors, however, may have also contributed to the baseline difference. Diabetes was more prevalent among patients who had a TURP-like procedure (22%) compared with patients who did not (12.3%; p=.0113). A pooled analysis reports that males with diabetes have a significantly increased risk of urinary incontinence (odds ratio=1.4; CI, 1.1-1.6) [18]. Furthermore, ADT use was higher among the patients who underwent a TURP-like procedure (35.4%) compared with patients who did not (16.1%, p<.0001). Patients who received ADT have been reported as having decreased urinary function in comparison to patients undergoing other treatments, such as prostatectomy or radiation therapy [15]. After controlling for ADT, the patients with a prior TURP-like procedure still showed decreased urinary function compared with the general cohort. Importantly, in the present study, the time to TURP and the type of procedure that was used did not impact urinary incontinence scores.

The findings related to the specific questions in **Table 3** showing worse urinary incontinence and urinary irritative/obstructive symptoms over time are notable and may similarly be related to the effect of radiation on susceptible tissue after a TURP-like procedure. Incontinence related to leakage and dribbling requiring use of pads suggests that radiation may exacerbate inadequate sphincter function for these patients with a prior TURP-like procedure. Patients presenting with a prior TURP-like procedure should be made aware of these specific risks during consultation for proton therapy.

Patients with a prior TURP-like procedure experienced more toxicities than observed in earlier proton therapy studies and required various interventions. Most of these patients who experienced a grade 3 toxicity (n=13) required a subsequent TURP, dilation procedure, or catheterization after proton therapy, suggesting a grade 3 GU obstructive rather than a grade 3 GU incontinent pathology after radiation (interfering with ADL; intervention indicated, such as clamp or collagen injections). It is unclear why radiation has such varying effects on patients who underwent similar procedures, especially when none of the pretreatment factors were associated with grade 3 toxicity.

Conclusion

A history of prior TURP-like procedure was strongly associated with reduced QOL outcomes and a higher reported rate of GU toxicity in patients undergoing definitive treatment with proton therapy for prostate cancer. Realistic expectations regarding QOL and toxicity should be communicated to patients with a history of TURP or a TURP-like procedure during consultation for proton therapy. Additionally, these issues should also be considered in a patient contemplating a TURP-like procedure before definitive treatment of prostate cancer with radiation to relieve obstructive symptoms. These observations may guide development of future studies in this cohort.

Lee et al. (2016), *Int J Particle Ther*

523

ADDITIONAL INFORMATION AND DECLARATIONS

References

1. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, Gingrich JR, Wei JT, Gilhooly P, Grob BM, Nsouli I, Iyer P, Cartagena R, Snider G, Roehrborn C, Sharifi R, Blank W, Pandya P, Andriole GL, Culkin D, Wheeler T. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med*. 2012;367:203–13.

2. Morris WJ, Keyes M, Spadinger I, Kwan W, Liu M, McKenzie M, Pai H, Pickles T, Tyldesley S. Population-based 10-year oncologic outcomes after low-dose-rate brachytherapy for low-risk and intermediate-risk prostate cancer. *Cancer*. 2013; 119:1537–46.

3. Alicikus ZA, Yamada Y, Zhang Z, Pei X, Hunt M, Kollmeier M, Cox B, Zelefsky MJ. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. *Cancer*. 2011;117:1429–37.

4. Luo HL, Fang FM, Chuang YC, Chiang PH. Previous transurethral resection of the prostate is not a contraindication to high-dose rate brachytherapy for prostate cancer. *BJU Int*. 2009;104:1620–3.

5. Devisetty K, Zorn KC, Katz MH, Jani AB, Liauw SL. External beam radiation therapy after transurethral resection of the prostate: a report on acute and late genitourinary toxicity. *Int J Radiat Oncol Biol Phys*. 2010;77:1060–5.

6. Hoppe B, Henderson R, Mendenhall WM, Nichols RC, Li Z, Mendenhall NP. Proton therapy for prostate cancer. *Oncology (Williston Park)*. 2011;25:644–50, 52.

7. Mendenhall NP, Li Z, Hoppe BS, Marcus RB, Jr., Mendenhall WM, Nichols RC, Morris CG, Williams CR, Costa J, Henderson R. Early outcomes from three prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012;82:213–21.

8. McGee L, Mendenhall NP, Henderson RH, Morris CG, Nichols RC, Jr., Marcus RJ, Jr., Li Z, Mendenhall WM, Williams CR, Hoppe BS. Outcomes in men with large prostates ($>/=$ 60 cm(3)) treated with definitive proton therapy for prostate cancer. *Acta Oncol*. 2013;52:470–6.

9. CTCAE. National Cancer Institute. Common Terminology Criteria for Adverse Events,

10. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology*. 2010;76:1245–50.

11. Korfage IJ, Roobol M, de Koning HJ, Kirkels WJ, Schroder FH, Essink-Bot ML. Does ''normal'' aging imply urinary, bowel, and erectile dysfunction? A general population survey. *Urology*. 2008;72:3–9.

12. Quander CR, Morris MC, Melson J, Bienias JL, Evans DA. Prevalence of and factors associated with fecal incontinence in a large community study of older individuals. *Am J Gastroenterol*. 2005;100:905–9.

13. Nakanishi N, Tatara K, Naramura H, Fujiwara H, Takashima Y, Fukuda H. Urinary and fecal incontinence in a community-residing older population in Japan. *J Am Geriatr Soc*. 1997;45:215–9.

14. Burke JP, Jacobson DJ, McGree ME, Nehra A, Roberts RO, Girman CJ, Lieber MM, Jacobsen SJ. Diabetes and sexual dysfunction: results from the Olmsted County study of urinary symptoms and health status among men. *J Urol*. 2007;177: 1438–42.

15. Lubeck DP, Grossfeld GD, Carroll PR. The effect of androgen deprivation therapy on health-related quality of life in men with prostate cancer. *Urology*. 2001;58:94–100.

16. Naslund MJ, Miner M. A review of the clinical efficacy and safety of 5alpha-reductase inhibitors for the enlarged prostate. *Clin Ther*. 2007;29:17–25.

17. Bruschini H, Simonetti R, Antunes AA, Srougi M. Urinary incontinence following surgery for BPH: the role of aging on the incidence of bladder dysfunction. *Int Braz J Urol*. 2011;37:380–6; discussion 7.

18. Shamliyan T, Wyman J, Bliss DZ, Kane RL, Wilt TJ. Prevention of urinary and fecal incontinence in adults. *Evid Rep Technol Assess (Full Rep)*. 2007:1–379.