Chapter 1: AUA Guideline on the Management of Benign Prostatic Hyperplasia: Diagnosis and Treatment Recommendations

Introduction

Benign prostatic hyperplasia (BPH), one of the most common diseases of aging men[2], can be associated with bothersome lower urinary tract symptoms (LUTS) that affect quality of life by interfering with normal daily activities and sleep patterns. The prevalence of histopathologic BPH is age dependent, with initial development usually after 40 years of age[3]. By 60 years of age, its prevalence is greater than 50% and by age 85 is as high as 90%. Similar to that of histologic evidence, the prevalence of bothersome symptoms also increases with age. Approximately one half of all men who have a histologic diagnosis have moderate to severe LUTS[2].

Because long-term data from population-based studies have only recently become available, the risks of developing complications and morbidities from untreated BPH are unclear. For example, despite recent evidence, there is still uncertainty regarding the likelihood that a patient with a specific symptom complex will develop complete urinary retention within a particular time frame. Nonetheless, BPH-associated mortality is rare in the United States, and serious complications are uncommon. In contrast, LUTS are bothersome to many patients, and the amount of bother may differ greatly among individuals with the same degree of symptom frequency and severity [4]. Since the impact of LUTS on the patient's quality of life is highly variable and not directly related to any measurable physiological factors, the patient's perception of the severity of the condition, as well as the degree to which it interferes with his lifestyle or causes embarrassment, should be the primary consideration in choosing therapy [5,6].

In the past decade, there have been significant changes in the available treatment options for BPH. New forms of medical and minimally invasive treatments have been approved by the United States Food and Drug Administration (FDA) while other therapies have become obsolete. This update of the 1994 AHCPR benign prostatic hyperplasia clinical practice guideline produced by the Agency for Health Care Policy and Research of the United States Department of Health and Human Services (AHCPR; now known as the Agency for Healthcare Research and Quality) was developed by a panel of experts (hereafter the Panel) chosen by the American Urological Association (AUA) Practice Guidelines Committee. Using an evidence-based approach, the multidisciplinary Panel focused on providing scientifically based information on currently available BPH treatment modalities. Because the Panel strongly believes that the patient should play a central role in determining his need for treatment, it set out to address the issue of whether or not there was sufficient evidence for outcomes (both benefits and risks) to be estimated. Thus, this guideline is intended to provide scientifically based information on treatment outcomes so that physicians can assist their patients in making appropriate treatment decisions.

Definitions and terminology

Benign prostatic hyperplasia is defined histologically as a disease process characterized by stromal and epithelial cell hyperplasia beginning in the periurethral zone of the prostate [7,8]. The chief complaint of the patient with BPH is usually bothersome LUTS typified by urinary frequency, urgency, nocturia, decreased and intermittent force of stream and the sensation of incomplete bladder emptying. The relationship between BPH and LUTS is complex, however, because not all men with histological evidence of BPH will develop LUTS. In addition, LUTS are neither specific to nor exclusive of BPH; other conditions in the lower urinary tract and

elsewhere may be causative. Moreover, not all patients with BPH and LUTS will have prostate enlargement, and prostate enlargement may exist in the absence of LUTS. The 4th International Consultation on BPH recommended the use of the general terminology LUTS or "LUTS suggestive of BPH" in place of the older term "prostatism" until a cause-and-effect BPH-symptom relationship has been established [9]. Recognizing the complexities of this nomenclature, the Panel decided that the term "BPH" would be used in this document when referring to any symptomatic conditions characterized by bothersome LUTS attributed to histological hyperplasia or increased tone of the prostate.

Methodology

As in the development of the 1994 AHCPR guideline, a systematic literature review was conducted based on the results of a MEDLINE® search. The search, which spanned the years from 1991 through early 2000, was supplemented with additional references from Panel members and additional data obtained from authors to explicate data previously published. The Panel chairmen reviewed the search results, and data were extracted to forms and entered into databases from which evidence tables were generated. After review by the Panel, some studies were excluded from additional analysis because of lack of relevance or quality problems.

The Panel had two principal tasks:

- to determine whether or not there was convincing scientific evidence that the benefits of a given treatment option (primarily symptom improvement) outweighed the risks (adverse events); and
- to explicitly define the primary outcomes of the recommended treatment options to assist patients and physicians in an informed decision-making process.

The Panel also outlined recommendations for future clinical research priorities.

Data on efficacy and safety of the following BPH treatments were reviewed: watchful waiting, alpha-adrenergic blocker therapy, 5 alpha-reductase inhibitor therapy, transurethral microwave heat treatment, transurethral needle ablation (TUNA®), interstitial laser therapy, stents, and various forms of transurethral surgery and open surgery. In addition, data on emerging transurethral heat-based technologies and high-intensity focused ultrasound (HIFU) were examined. The published literature on phytotherapy was also evaluated, although there were few randomized clinical trials of suitable duration to allow comment.

Detailed analysis of study outcomes using a variety of meta-analytic techniques was performed, and outcomes tables were created for Panel review. Treatment recommendations were based on these outcomes tables and tempered by the Panel's expert opinion. Key evidence for some interventions became available after the outcomes analysis was complete. The Panel directly reviewed these data and agreed that the new information should be considered for inclusion in the guideline. Thus, evidence from several studies support recommendations made by Panel consensus; however, these data are not presented as outcomes estimates.

Of note, FDA approval alone was not sufficient to justify a positive recommendation in this guideline. First, FDA approval may be requested by a manufacturer for a non-BPH indication because a specific BPH indication may be more complicated and expensive to attain. Second, FDA approval may precede the publication of key pivotal studies, precluding Panel analysis. Third, FDA approval once given does not imply that the intervention is still currently recommended or even available (e.g., balloon dilation). Finally, the FDA may have approved a treatment that the Panel believes is not appropriate given the other available treatment options.

This guideline was drafted, reviewed by the Panel, then examined by 58 peer reviewers, and finally approved by the Practice Guidelines Committee and the Board of Directors of the AUA.

A full description of the methodology is presented in Chapter 2 and in the Methodologic Appendix (Appendix 2-C) of this guideline.

As in the 1994 AHCPR guideline, the Panel generated recommendations based on the strength of the evidence for both diagnostic and treatment modalities and the expected amount of variation in patient preferences for treatments. In some cases, recommendations were supported solely by the Panel's expert opinion and are designated as such in the text. For diagnostic tests, the Panel utilized the terms "recommended," "optional," and "not recommended" to indicate the desirability of specific diagnostics. Treatment recommendations were graded according to three levels of flexibility [10, 11]. For treatments, the term "standard" is the least flexible of the three, a "guideline" is more flexible, and an "option" is the most flexible. Options can exist because of insufficient evidence or because patient preferences are divided. (The grading of both diagnostic and treatment recommendations is detailed in Chapter 2.)

The 1994 AHCPR guideline defined an Index Patient (the specific type of patient to whom the recommendations applied) in recognition of the differences in decision making that depend upon patient circumstances. Similarly, these diagnostic and treatment guidelines pertain only to men over the age of 50 without significant risk (as ascertained by history) of non-BPH causes of LUTS. Men with polyuria, underlying neurologic disease, or prior lower urinary tract disease and younger men with voiding dysfunction will require more extensive evaluation. These important causes of voiding function are not specifically addressed in this guideline.

Diagnostic evaluation of benign prostatic hyperplasia

Upon review of the diagnostic recommendations in the 1994 AHCPR guideline, the Panel decided that an evidence-based update was not necessary. The Panel unanimously agreed that the

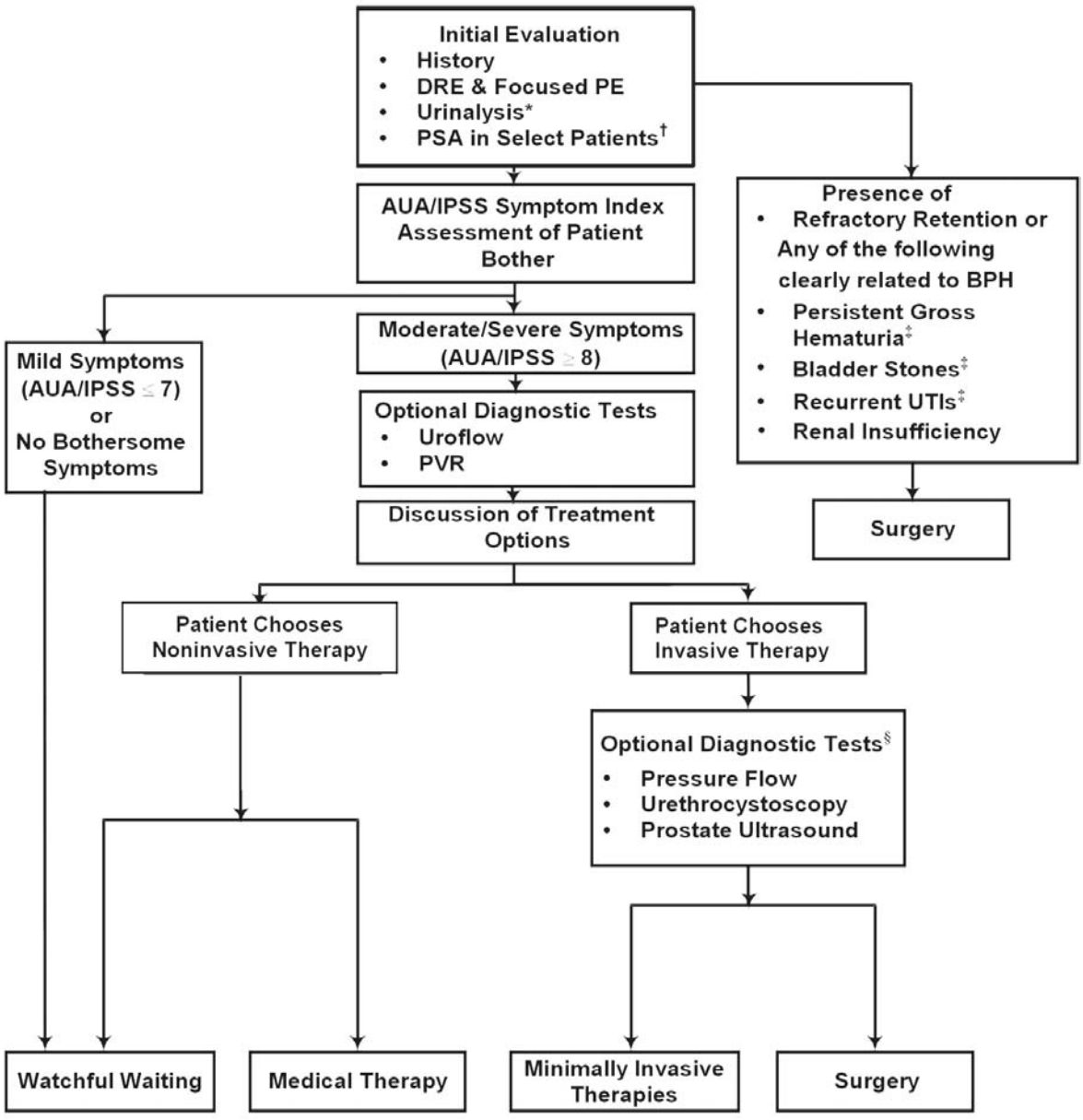
prior recommendations and decision diagram for diagnosis were still valid and reflective of "best practice" with five exceptions, which were derived from the Panel's expert opinion:

- **Serum prostate-specific antigen (PSA) measurement is recommended in select patients;**
- **Urine cytology is recommended as an option in men with predominantly irritative symptoms;**
- **Other validated symptom assessment instruments are supplementary to the AUA Symptom Score;**
- **Serum creatinine measurement is no longer recommended on initial evaluation in the standard patient; and**
- **Discussion of treatment options with the patient is recommended before pressure-flow testing is performed.**

The 1994 diagnostic guidelines, with italicized revisions, are revisited below using the previously referenced studies from that publication.

An algorithm (Figure 1.1) is provided as a framework for diagnosis and treatment and not as a rigid pathway that must be followed in all cases. Individual patients will present for whom deviations from these policies are appropriate. In such circumstances, the clinician should exercise clinical judgment and act in the patient's best interest.

Figure 1.1. Benign prostatic hyperplasia (BPH) diagnosis and treatment



*In patients with clinically significant prostatic bleeding, a course of a 5 alpha-reductase inhibitor may be used. If bleeding persists, tissue ablative surgery is indicated.
†Patients with at least a 10-year life expectancy for whom knowledge of the presence of prostate cancer would change management or patients for whom the PSA measurement may change the management of voiding symptoms.
‡After exhausting other therapeutic options as discussed in detail in the text.
§Some diagnostic tests are used in predicting response to therapy. Pressure-flow studies are most useful in men prior to surgery.

AUA, American Urological Association; DRE, digital rectal exam; IPSS, International Prostate Symptom Score; PE, physical exam; PSA, prostate-specific antigen; PVR, postvoid residual urine; UTI, urinary tract infection.

Initial Evaluation

Lower urinary tract pathologies in aging men produce similar, if not identical, symptoms. Therefore, the challenge in patients with LUTS is to establish that the symptoms are due to BPH. Nonprostatic causes of symptoms can be excluded in a significant number of patients on the basis of a medical history, physical examination, and urinalysis.

Recommended: In the initial evaluation of all patients presenting with LUTS suggestive of BPH:

- **A medical history should be taken to identify other causes of voiding dysfunction or comorbidities that may complicate treatment.**

The medical history should focus on the urinary tract, previous surgical procedures, and general health issues, specifically, medical conditions and symptoms that lead to bladder dysfunction or excessive urine production (polyuria), family history of prostate disease (BPH and cancer), and fitness for possible surgical procedures. Patient voiding diaries, where the frequency of micturition and urine volume is recorded, may be helpful in selected patients, especially in those with nocturia as the predominant symptom.

- **A physical examination, including both a digital rectal examination (DRE) and a focused neurologic examination, should be performed.**

The presence of locally advanced prostate cancer, which also can produce LUTS, should be excluded by DRE. Digital rectal exam tends to underestimate true prostate size: if the prostate feels large by DRE, it usually also is found to be enlarged by ultrasound or other measurement techniques [12, 13]. A focused neurologic examination should assess the patient's general mental status, ambulatory status, lower extremity neuromuscular function, and anal sphincter tone.

- **A urinalysis should be performed by dipstick testing or microscopic examination of the sediment to screen for hematuria and urinary tract infection (UTI).**

Bladder cancer, carcinoma in situ of the bladder, UTIs, urethral strictures, distal urethral stones, and bladder stones can produce LUTS in aging men. Although hematuria or pyuria is not universally present in these conditions, a normal urine examination makes these diagnoses less likely [14-17].

- ***Measurement of the serum prostate-specific antigen (PSA) should be offered to the following patients: 1) those with at least a 10-year life expectancy and for whom knowledge of the presence of prostate cancer would change management; or 2) those for whom the PSA measurement may change the management of their voiding symptoms.***

Serum PSA is one predictor of the natural history of BPH — men with higher serum PSA levels have a higher risk of future growth of the prostate, symptom and flow rate deterioration, acute urinary retention, and BPH-related surgery [18-20]. This recommendation does not address the value of PSA screening in the testing of asymptomatic men in the general population. Rather, because prostate cancer is one of the potential causes of LUTS in aging men, PSA (together with DRE) is a relatively sensitive way to exclude prostate cancer as a diagnosis [21-23]. Physician and patient concern, however, lies with the specificity of the test—approximately 25 % of men with BPH have a serum PSA greater than 4 ng/mL. Because of the overlap between serum PSA values in men with BPH and those with clinically localized prostate cancer, PSA velocity (PSAV), free/total PSA ratio, complexed PSA (cPSA), and PSA density (PSAD) measurements may help improve diagnostic specificity [24, 25].

The benefits and risks of PSA testing should be discussed with the patient. In most patients, a normal DRE should be sufficient to exclude locally advanced cancer as a cause of voiding dysfunction. Prostate-specific antigen testing is most appropriate for patients likely to have a natural life span greater than 10 years and in whom the known presence of prostate cancer would

change management or for whom the PSA measurement may change the management of the patient's voiding symptoms. [This recommendation is based on the Panel's expert opinion.]

> ***Optional: Urine cytology may be considered in men with a predominance of irritative symptoms, especially with a history of smoking or other risk factors, to aid in the diagnosis of bladder carcinoma in situ and bladder cancer.***
>
> ***Not recommended: The routine measurement of serum creatinine levels is not indicated in the initial evaluation of men with LUTS secondary to BPH.***

Baseline renal insufficiency appears to be no more common in men with BPH than in men of the same age group in the general population. The Panel reviewed the experience in several large BPH clinical trial databases that have more than 10,000 patient-years of follow-up. Renal insufficiency has been reported in well under 1 % of patients in these studies and is commonly secondary to non-BPH causes (e.g., diabetic nephropathy). Moreover, in the MTOPS trial (Medical Therapy of Prostatic Symptoms), 81 out of 4394 (1.8%) men screened for participation were excluded due to renal or hepatic impairment, defined as serum creatinine >2 mg/dL or significant liver enzyme abnormalities, respectively. No information is available regarding the number of patients whose renal insufficiency was due to BPH versus other causes; thus, the number of men presenting with renal insufficiency due to BPH is most likely also under 1%. If urinalysis and/or history and physical examination suggest underlying renal disease or urinary retention, measurement of serum creatinine also may be necessary prior to the performance of renal imaging studies that require intravenous contrast. [These recommendations are based on the Panel's expert opinion.]

Symptom Assessment

> **Recommended: The AUA Symptom Index (identical to the seven symptom questions of the International Prostate Symptom Score [IPSS]) should be**

used as the symptom-scoring instrument in the initial assessment of each patient presenting with BPH.

Most patients who seek treatment for BPH do so because symptoms alter quality of life. Symptom quantification is therefore of major importance in determining the severity of disease, in documenting the response to therapy, and in detecting symptom progression in men managed by watchful waiting. The AUA Symptom Index (see Appendix 1-A) or the identical IPSS is recommended for symptom assessment in each patient presenting with BPH because it is superior to an unstructured interview in quantifying symptom frequency and severity. Using seven questions that relate to associated symptoms[2], classification ranges from mild (0 to 7) to moderate (8 to 19) or severe (20 to 35) [26, 27]. Some patients may require an explanation of the questions to adequately understand their intent. Although validated for its clarity, test/retest reliability, internal consistency, and criteria strength, this tool is not a replacement for personal discussion of symptoms with the patient.

Symptom score changes and the degree of each patient's bother due to the symptoms should be the primary determinants of treatment response or disease progression in the follow-up period. However, symptom scores alone do not delineate the morbidity of a prostate problem as perceived by the individual patient. An intervention may be more logical for a moderately symptomatic patient who finds his symptoms bothersome than for a severely symptomatic patient who finds his symptoms tolerable.

Optional: Other validated assessment instruments addressing the frequency or severity of LUTS in men with BPH, bother due to symptoms, interference with daily activities, urinary continence, sexual functioning and health-related general or disease-specific quality of life may be administered.

Examples of these instruments are the International Continence Society male questionnaire [28] and the Danish Prostatic Symptom Score [29], which measure symptom severity and frequency; the

BPH Impact Index (Appendix 1-B) [4,] which measures the impact of symptoms on activities of daily living and their level of interference; and the Disease Specific Quality of Life (QoL) question of the IPSS (Appendix 1-A), which measures quality of life as it is impacted and impaired by BPH. Baseline sexual function, treatment choices, and/or impact of treatment are measured by sexual function questionnaires. [These recommendations are based on Panel expert opinion.]

Optional Diagnostic Tests

Optional tests are those that are not required but may aid in the decision-making process. When the initial evaluation suggests a nonprostatic cause for the patient's symptoms or when the patient selects invasive therapy, the physician may consider additional diagnostic testing if the results of the test(s) are likely to change the patient's management or more precisely predict the benefits and risks of the selected treatment. The 1994 AHCPR guideline suggested that the physician consider performing one or more "optional" diagnostic tests prior to offering treatment options to the patient [1]. In some cases, additional diagnostic tests may aid in the selection of an invasive treatment that is best for an individual patient (e.g., identification of prostate middle lobe). The 2001 5th International Consultation on BPH, cosponsored by the World Health Organization, also deemed flow rate and postvoid residual urine (PVR) volume to be optional tests for men who were considering therapy for bothersome LUTS.

> **Optional: Following the initial evaluation of the patient, urinary flow-rate recording and measurement of postvoid residual urine (PVR) may be appropriate. These tests usually are not necessary prior to the institution of watchful waiting or medical therapy. However, they may be helpful in patients with a complex medical history (e.g., neurologic or other diseases known to affect bladder function or prior failure of BPH therapy) and in those desiring invasive therapy.**

Urinary flow-rate recording (uroflowmetry), specifically Qmax, may predict the response to surgery and, to a lesser degree, the natural history of the disease. Men with LUTS and normal Qmax are more likely to have a non-BPH-related cause of their symptoms. Nevertheless, the symptom response to many therapies, specifically alpha blockers, is not dependent upon baseline flow rate. Men with a Qmax less than 10 mL/sec are more likely to have urodynamic obstruction and are therefore more likely to improve with surgery. Men with normal flow rates but significant urinary symptoms are more likely to have nonprostatic causes for those symptoms requiring more extensive investigation. Urinary flow rate, though, predicts less well the response to medical therapy or the failure of watchful waiting. Because of test-retest variability and a lack of appropriately designed outcome studies, it is not feasible to establish a flow-rate "cut-point" for decision making.

Large **PVR** volumes (e.g., 350 mL) may indicate bladder dysfunction and predict a slightly less favorable response to treatment. In addition, large PVRs may herald progression of disease. Still, residual urine is not a contraindication to watchful waiting or medical therapy. Because of large test-retest variability and a lack of appropriately designed outcome studies, it is not feasible to establish a PVR "cut-point" for decision making. The Panel considered the use of PVR measurements optional in men undergoing noninvasive therapy based on the observation that the safety of noninvasive therapy has not been documented in patients with residual urine (200 to 300 mL). In some studies, however, residual urine has predicted a high failure rate of watchful waiting [30]. Within the range of residual urine values from 0 to 300 mL, the PVR does not predict the response to medical therapy. Although long-term, controlled data are lacking, many patients maintain fairly large amounts of residual urine without evidence of UTI, renal insufficiency, or

bothersome symptoms. Therefore, no level of residual urine, in and of itself, mandates invasive therapy.

Initial management and discussion of treatment options with the patients

Management of Patients With Mild Symptoms or Moderate to Severe Symptoms Without Bother

> **Standard: Patients with mild symptoms of BPH (AUA Symptom Score ≤7) and patients with moderate or severe symptoms (AUA Symptom Score ≥ 8) who are not bothered by their symptoms (i.e., they do not interfere with the daily activities of living) should be managed using a strategy of watchful waiting.**

From the initial evaluation, the physician should determine whether the patient has developed a serious complication of BPH that would direct treatment toward surgical options. Patients with only mild symptoms or moderate to severe symptoms that are not bothersome generally will not benefit from therapy because these symptoms do not significantly impact quality of life [31, 25, 26]. In addition, the risks of medical therapy outweigh the benefits of symptom improvement in this group of men. Therefore, the Panel felt that the recommendation presented above, from the 1994 AHCPR guideline, was still appropriate with one modification, which is the inclusion of men with "nonbothersome" symptoms in the "mild" category. Men who have moderate to severe symptom frequency and severity but are not bothered by their symptoms should not be considered for further diagnostic tests or active treatment.

Management of Patients With Bothersome Moderate to Severe Symptoms

> **Option: Treatment options for patients with bothersome moderate to severe symptoms of BPH (AUA Symptom Score ≥ 8) include watchful waiting and the medical, minimally invasive, or surgical therapies defined in Table 1.1.**

Guideline: Information on the benefits and harms of the BPH treatment options (including watchful waiting) should be explained to patients with moderate to severe symptoms (AUA Symptom Score ≥ 8) who are bothered enough to consider therapy.

The degree to which BPH patients are bothered by LUTS varies among individual patients with the same level of symptoms, although in general the level of bother and interference will increase with the level of symptom severity [32]. Although patients with mild symptoms or mild to severe symptoms that are not bothersome prefer watchful waiting, there is a wide range of preference in patients with bothersome moderate to severe symptoms [1]. Therefore, the "best" treatment from the patient's viewpoint may differ from that believed by the physician to be the most efficacious treatment. Patients may prefer less effective therapy if it also has less risk or cost. Treatment options—watchful waiting and medical, minimally invasive or surgical therapies—are defined in Table 1.1, and information on their harms and benefits is presented in the Simplified Outcomes Tables (Appendix 1-C).

Table 1.1. Treatment options for patients with moderate to severe symptoms of benign prostatic hyperplasia

Watchful Waiting
Medical Therapies
Alpha-adrenergic blockers
Alfuzosin
Doxazosin
Tamsulosin
Terazosin
5 Alpha-reductase inhibitors
Dutasteride*
Finasteride
Combination therapy (alpha blocker and 5 alpha-reductase inhibitor)*†
Minimally Invasive Therapies
Transurethral microwave heat treatments
CoreTherm™*
Prostatron® (various versions)
Targis®
TherMatrx™*
Transurethral needle ablation
UroLume® stent‡
Surgical Therapies
Transurethral resection of the prostate
Transurethral electrovaporization
Transurethral incision of the prostate
Transurethral holmium laser resection/enucleation
Transurethral laser vaporization
Transurethral laser coagulation (e.g., visual laser ablation)
Open prostatectomy

*Recommendations based on randomized, controlled trials not included in the outcomes tables.

†The Panel assumes that the combination of any effective alpha blocker and 5 alpha-reductase inhibitor probably produces a comparable benefit. However, the best-tested combination is doxazosin and finasteride. The safety of specific combinations other than finasteride plus doxazosin, terazosin, and alfuzosin has not been assessed.

‡Recommended for a subset of patients, see text.

At this point, the benefits and risks of all therapeutic interventions should be discussed with the patient using the Simplified Outcomes Tables presented in Appendix 1-C. It is appropriate for patients with moderate symptoms and bother to choose watchful waiting if they feel that the benefits outweigh the risks of an active therapy. Patients choosing medical therapies may be prescribed the most appropriate agent(s) at this time without additional testing. Patients choosing invasive therapies may benefit from additional optional diagnostic tests.

Optional Diagnostic Tests for Patients Who Choose Invasive Therapy

Determining the relative significance of performing certain diagnostic tests prior to treatment initiation has been a complex task. In the BPH clinical trial setting, eligibility criteria usually exclude patients whose diagnostic test measurements exceed certain limits. Thus, the ability of a diagnostic test to predict natural history and outcomes in patients whose measurements are beyond these limits has not been fully elucidated. For example, if a BPH treatment trial only includes patients with a maximum flow rate of less than 12 mL/sec and residual urines of less than 250 mL, the outcomes of a patient with measurements greater than these limits are unknown.

There now is some evidence, however, to suggest that certain tests may be valuable in predicting the response to therapy in specific circumstances. Serum PSA measurement (as a proxy for prostate size) and ultrasound predict both the natural history and progression of LUTS and BPH and the therapeutic response to 5 alpha-reductase inhibitors. Because minimally invasive therapies and transurethral incision of the prostate (TUIP) are only effective in patients with prostates in a certain size range, the shape of the prostate (i.e., the presence of a middle lobe) also may predict response or lack thereof to certain minimally invasive or medical therapies. Although maximum flow-rate (a proxy for urodynamic studies) and invasive urodynamic studies have limited ability to predict both natural history and therapeutic response,

they have been shown to predict the response to surgery and, less so, minimally invasive therapies. The shape of the prostate as assessed by cystoscopy (e.g., lateral versus middle lobes) also may forecast the response to minimally invasive and surgical therapies. Finally, PVR measurement predicts both natural history and treatment response to all therapies to a limited extent.

> **Optional: Additional diagnostic tests, such as pressure-flow urodynamic studies, urethrocystoscopy and ultrasound (transrectal or transabdominal), are optional in patients choosing invasive therapies, particularly when the outcome of the pressure-flow study may impact choice of intervention or if prostate size and anatomical configuration are important considerations for a given treatment modality. They are not recommended in the initial evaluation of LUTS or in a setting other than those described above.**

A **pressure-flow urodynamic study,** although invasive, is the only test that directly measures the relative contribution of the bladder and bladder outlet and the contributions of the prostate to lower urinary tract function, dysfunction or symptoms. This study is not indicated to predict the response to medical therapy but is considered optional in men prior to invasive therapy. The 5th International Consultation on BPH recommends uroflowmetry for all men who choose invasive or minimally invasive therapy followed by pressure-flow studies in those men with a maximal urinary flow rate (Qmax) greater than 10 mL/sec when surgery is being considered [33]. Men with higher flow rates are less likely to be obstructed and, therefore, less likely to benefit from surgical therapy. Pressure-flow studies also may be considered in the evaluation of men with LUTS who have failed prior invasive therapy or who have concomitant neurologic disease known to affect bladder function (e.g., stroke, Parkinson's disease, and neuropathy). The benefit of this study rests primarily in men with concomitant neurologic

disease or a history of prior invasive therapy for BPH and in men in whom the physician believes that the study outcome would change the management strategy.

Urethrocystoscopy may be appropriate in men with a history of microscopic or gross hematuria, urethral stricture (or risk factors, such as history of urethritis or urethral injury), bladder cancer, or prior lower urinary tract surgery (especially transurethral resection of the prostate [TURP]). This test should not be used in the initial evaluation of patients without these risk factors or solely to determine the "need for treatment" and is not routinely necessary prior to watchful waiting or medical therapy. The endoscopic appearance of the prostatic urethra and bladder does not predict the response to BPH therapy. Nevertheless, the endoscopic appearance of the prostate anatomy may guide the choice of therapy in patients who have already decided to proceed with an invasive approach.

Transrectal or transabdominal prostate ultrasound may be an appropriate optional test when minimally invasive or surgical interventions are chosen as therapy. Ultrasound examinations are not routinely necessary prior to watchful waiting or medical therapy. The size and shape of the prostate are of importance in selecting patients for transurethral microwave heat treatment, TUNA and other minimally invasive therapies, as well as for the selection of TUIP versus TURP. Furthermore, anatomical features, such as intravesical lobes, may impact the choice of therapy. Prostate size, as measured by ultrasound, is predictive of the natural history of BPH and the response to therapy with 5 alpha-reductase inhibitors. However, some patients may have a serum PSA measurement performed as part of the initial evaluation, and serum PSA as a proxy for prostate volume is also a strong predictor of natural history and response to 5 alpha-reductase inhibitor therapy [18, 34].

Not Recommended: Filling cystometrography (CMG) and imaging of the upper urinary tract by ultrasonography or excretory urography are not

recommended in the evaluation of the typical patient with symptoms of BPH unless the patient has hematuria, UTI, renal insufficiency, or a history of urolithiasis or urinary tract surgery.

The role of CMG and upper tract imaging is thoroughly reviewed in the 1994 AHCPR guideline [1].

Treatment recommendations

In the first half of the 20th century, two treatment approaches, both surgical, were available for BPH—open prostatectomy and TURP. With improvements such as fiber-optic lighting and the Hopkins rod lens wide-angle system [35], TURP became the preferred treatment, not only for severe conditions secondary to BPH, such as urinary retention and hydronephrosis, but for less severe yet bothersome symptoms, such as urgency and frequency [36]. Currently, at the beginning of this new century, TURP is still the benchmark therapy for BPH[36].

Nonetheless, there are now many acceptable alternatives to TURP that are less costly per treatment episode, that require less time to produce positive outcomes, and that have less associated morbidity. These alternatives, which are listed in Tables 1.1 and 1.2, include medical therapies, such as alpha-adrenergic blockers, the minimally invasive options, such as transurethral microwave thermotherapy (TUMT®), and the commonly utilized investigational treatments, offer patients a range of choices based on the degree of their symptoms and the presence of uncommon or serious complications.

A brief discussion of these treatment options is provided in the following sections, and Chapter 3 provides the results of the evidence-based, comparative outcomes analyses of these therapies to the extent that the outcomes evidence was available.

Recommended Therapies

Watchful Waiting

Watchful waiting is the preferred management strategy for patients with mild symptoms. It is also an appropriate option for men with moderate to severe symptoms who have not yet developed complications of BPH (e.g., renal insufficiency, urinary retention or recurrent infection).

Watchful waiting is a management strategy in which the patient is monitored by his physician but receives no active intervention for BPH. The level of symptom distress that individual patients are able to tolerate is highly variable so that watchful waiting may be a patient's treatment of choice even if he has a high AUA Symptom Index or IPSS score [9, 37]. Symptom distress may be reduced with such simple measures as decreasing fluid intake at bedtime and decreasing caffeine and alcohol intake generally. Watchful-waiting patients usually are reexamined yearly, repeating the initial evaluation outlined in Figure 1.1.

As prostate volume assessed by DRE and/or serum PSA predicts the natural history of symptoms, flow rate, and risk for acute urinary retention and surgery, patients may be advised as to their individual risk depending on the outcomes of these assessments. Measures to reduce the risk, such as medical intervention, may be offered depending on the circumstances.

Medical Treatment

The medical therapies for BPH examined by the Panel were alpha-adrenergic blockers, 5 alpha-reductase inhibitors, combination therapies, and phytotherapy (use of plant extracts). Medical therapies are not as efficacious as surgical therapies but may provide adequate symptom relief with fewer and less serious associated adverse events [38, 37].

Alpha-adrenergic blocker therapy

Option: Alfuzosin, doxazosin, tamsulosin and terazosin are appropriate treatment options for patients with LUTS secondary to BPH. Although there are slight differences in the adverse-event profiles of these agents, the Panel believes that all four agents have equal clinical effectiveness.

Guideline: Data are insufficient to support a recommendation for the use of prazosin or the nonselective alpha blocker phenoxybenzamine as treatment options for LUTS secondary to BPH. [The recommendation concerning phenoxybenzamine is based on Panel expert opinion.]

Alpha-blocker therapy is based on the hypothesis that clinical BPH is partly caused by $alpha_1$-adrenergic-mediated contraction of prostatic smooth muscle, resulting in bladder outlet obstruction [39, 40]. Alpha-adrenergic receptor antagonists (blockers) such as doxazosin, tamsulosin, alfuzosin, and terazosin inhibit this process and thus relieve the bladder outlet obstruction[41].

The use of alfuzosin, doxazosin, tamsulosin, and terazosin has been extensively investigated for the treatment of LUTS. Lepor [37] notes that efficacy is dose dependent for the titratable alpha blockers doxazosin and terazosin —the higher the dose, the greater the observed improvement. Maximum tolerable and effective doses have not been defined for any alpha blocker, but reported clinical data support the efficacy and safety of titrating patients to 8 mg of doxazosin, to 0.8 mg of tamsulosin (from 0.4 mg), and to 10 mg of terazosin. The primary adverse events reported with alpha-blocker therapy are orthostatic hypotension, dizziness, tiredness (asthenia), ejaculatory problems, and nasal congestion. Meta-analyzed data from the Panel's evidence-based review suggest that alfuzosin, doxazosin, tamsulosin, and terazosin are similarly effective in partially relieving symptoms, producing on average a 4-to-6 point improvement in the AUA Symptom Index. In general, patients will perceive this level of symptom improvement as a

meaningful change[42]. Trials directly comparing alpha blockers either are of short duration, or use inappropriate dosages or nonstandardized outcome measures [43-46]. However, the Panel did use Bayesian techniques to create such comparisons using the data that compare each of the alpha blockers with placebo. The resulting comparisons are detailed in Chapter 3. The adverse event profile appears slightly different between the four alpha-blocking agents, for example, tamsulosin appears to have a lower probability of orthostatic hypotension but a higher probability of ejaculatory dysfunction than the other alpha blockers. Large, well-designed, direct comparator trials are needed to substantiate claims of superior safety.

In men with hypertension and cardiac risk factors, doxazosin monotherapy was associated with a higher incidence of congestive heart failure than seen with other antihypertensive agents[47]. Based upon these findings, use of an alpha blocker to manage a patient's LUTS should not necessarily be assumed to constitute optimal management of the patient's concomitant hypertension. In these cases, patients with hypertension may require separate management of their hypertension.

5 Alpha-reductase inhibitor therapy

Option: The 5 alpha-reductase inhibitors finasteride and dutasteride are appropriate and effective treatments for patients with LUTS associated with demonstrable prostatic enlargement.

Option: Patients with symptomatic prostatic enlargement but without signs of bother may be offered a 5 alpha-reductase inhibitor to prevent progression of the disease. However, the disadvantages of this therapeutic approach (e.g., side effects such as sexual dysfunction) and the need for long-term daily therapy should be presented to the patient in comparison to a reasonable estimate of his baseline risk of progression (i.e., retention and the risks associated with BPH-related surgery) so that an informed decision can be made.

Guideline: 5 Alpha-reductase inhibitors are not appropriate treatments for men with LUTS who do not have evidence of prostatic enlargement.

Finasteride (and other 5 alpha-reductase inhibitors shown in randomized, clinical trials to be equally effective in reducing prostatic size) is an appropriate BPH treatment option. Finasteride is less effective than an alpha blocker in improving LUTS and is not an appropriate treatment for men with LUTS who do not have prostatic enlargement. Finasteride reduces the risk of acute urinary retention and the need for BPH-related surgery[18].

A 5 alpha-reductase inhibitor is the sole hormonal therapy, to date, that demonstrates both efficacy and acceptable safety for treatment of BPH[48]. Finasteride can reduce the size of the prostate, can increase peak urinary flow rate, and can reduce BPH symptoms[49]. It lowers serum and intraprostatic dihydrotestosterone, but not to castration levels, and lowers serum PSA, but does not mask the PSA-based detection of prostate cancer. With finasteride, the average patient experiences a 3-point improvement in the AUA Symptom Index. In general, patients will perceive this level of symptom improvement as a meaningful change[42]. Finasteride is ineffective in patients who do not have enlarged prostates [48, 41]. Reported adverse events are primarily sexually related and include decreased libido, ejaculatory dysfunction, and erectile dysfunction and are reversible and uncommon after the first year of therapy.

The Panel's evidence-based review determined that a 5 alpha-reductase inhibitor is effective in partially relieving symptoms but is less effective for this purpose than alpha-blocker therapy. Symptom score improvement is not significantly greater in men with large prostates. However, due to the more progressive nature of the disease in men with larger glands and/or higher PSA values, conservatively treated patients (watchful waiting or placebo groups) face an increasingly worse prognosis, enhancing the difference over time in outcomes between finasteride and no treatment or placebo groups. Finasteride reduces the risk of subsequent acute urinary retention

and the need for BPH-related surgery with the absolute benefit increasing with rising prostate volume or serum PSA [18, 20, 34].

The new 5 alpha-reductase inhibitor dutasteride has been shown to be of similar efficacy as finasteride in terms of symptom score and flow-rate improvement, as well as in the prevention of disease progression, while having a comparable safety profile[50].

Combination therapy

[Disclosure: The recommendations in this section are based on the meta-analysis of published data presented herein as well as on new data in press or currently being prepared for publication[51]. The scientific quality and importance of these new study findings support the use of their outcomes in formulating the recommendations for combination therapy.]

> **Option: The combination of an alpha-adrenergic receptor blocker and a 5 alpha-reductase inhibitor (combination therapy) is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement.** [This recommendation is based on Panel consensus.]

In studies of up to one-year duration, the combination of an alpha-adrenergic blocker and a 5 alpha-reductase inhibitor has been found to be no more effective in treating symptoms than an alpha blocker alone [52, 53, 41]. However, in a recently completed 5-year study, the combination therapy appeared to be more effective in relieving and preventing the progression of symptoms than alpha-blocker monotherapy[51]. Furthermore, the addition of a 5 alpha-reductase inhibitor to an alpha blocker significantly reduced the long-term risk of acute urinary retention and the need for BPH-related surgery. The overall risk of progression, mostly due to symptomatic progression, was reduced by 39% for doxazosin, 34% for finasteride and 67% for combination therapy. The risk of retention was reduced by 31% for doxazosin, 67% for finasteride, and 79% for combination therapy while the risk of surgery was reduced by 64% and 67% for finasteride

and combination therapy, respectively, with no significant change in risk noted in the doxazosin group compared to placebo. The overall probability of these risks, their relative reduction over time by therapy, and their impact on quality of life, though, must be weighed against the cost of combination therapy in an individual patient. Patients most likely to benefit from combination therapy are those in whom baseline risk of progression is significantly higher, in general, than in patients with larger glands and higher PSA values. At present, absolute threshold values cannot be given because they are based on personal risk assessment, the patient's desire to avoid surgery, and the economic circumstances of the patient and the health care system. Adverse events reported with the use of combination therapy reflect the combined adverse-event profiles of both alpha blockers and 5 alpha-reductase inhibitors.

The Panel assumes that the combination of any effective alpha blocker and 5 alpha-reductase inhibitor probably produces a comparable benefit. Still, the best-tested combination is doxazosin and finasteride. The safety of specific combinations other than finasteride plus doxazosin, terazosin, and alfuzosin has not been assessed.

Minimally Invasive Therapies

At the time of the initial literature search, the Panel found evidence that established the use of a number of minimally invasive therapies for the treatment of BPH. A thorough review of the efficacy data supports the inclusion of the following technologies as treatment options: Prostatron® (Prostasoft® 2.0 and 2.5; Urologix, Minneapolis, Minnesota); the Targis® device (Urologix, Minneapolis, Minnesota); TUNA (Medtronics, Minneapolis, Minnesota); and the UroLume Endoprosthesis Stent (American Medical Systems, Minnetonka, Minnesota). As discussed later, the UroLume stent is not a treatment alternative for the standard patient.

The available evidence was inadequate to support inclusion of the following technologies as treatment options at this time: HIFU (Ablatherm®, EDAP Technomed, France) [54] and interstitial

laser coagulation (ILC; Indigo Optima Laser System, Ethicon Endo-Surgery, Cincinnati, Ohio) [55, 56]. These treatments have not been subjected to rigorous prospective, multicenter, controlled trials.

Similarly, only one multinational, uncontrolled study was found as evidence for the efficacy and safety of water-induced thermal therapy (WIT; Thermoflex® System, ACMI, Southborough, Massachusetts), also an FDA-approved modality for the treatment of BPH[57]. More recently, favorable results were again reported with the use of WIT but also in an uncontrolled, single-center setting[58]. At present, WIT is available in the United States.

In their post hoc literature search and review, the Panel found published randomized, controlled trials supporting the efficacy and safety of both the CoreTherm™ (Prostalund, Lund, Sweden) [59] and TherMatrx™ (TherMatrx, Inc., Northbrook, Illinois) [60] devices. These products received FDA approval in 2002 and currently are available in the United States.

Thermal-based therapies

Thermal-based therapies use high temperatures to produce coagulation necrosis of prostate tissue, attempting to achieve results with heat that are similar to those achieved by TURP but at lower cost and morbidity. Although microwaves have been the primary means to heat prostatic tissue, radio frequency (RF) waves, high-intensity ultrasound [61-63], hot water (e.g., WIT) and interstitial laser have been used for the same purpose. A thermal-based therapy achieving temperatures greater than 45°C is referred to as *thermotherapy*, and treatment to temperatures below 45°C is referred to as *hyperthermia*. Temperatures in excess of 45°C to 50°C are known to produce tissue coagulation, but temperatures in the hyperthermia range have no clearly demonstrable prostatic tissue effects. The principles underlying the use of hyperthermia were validated in the cancer model system (i.e., that neoplastic cells are more sensitive to slight elevations of temperature than normal cells) and may not be operational in the benign

hyperplastic prostate[62]. Several clinical trials have been performed with both transurethral and transrectal hyperthermia. Matzkin [64], in his review of 32 studies, concluded that hyperthermia had not yet been proven effective in achieving lasting benefits. A large multicenter, sham-controlled trial conducted in the early 1990s in the Paris Public Hospital System found neither transurethral nor transrectal hyperthermia superior to sham treatment in terms of symptom improvement in men with BPH[65].

Transurethral microwave heat treatment

Option: The following transurethral microwave heat treatments are effective in partially relieving symptoms in men with BPH: Prostatron®, Targis®, CoreTherm™, and TherMatrx™. There is no evidence from direct comparator trials to suggest superiority of one specific device over another.

First studied for the treatment of BPH under an FDA-approved protocol in 1991, the development of transurethral microwave heat treatment was partially prompted by the failure of the transrectal or transurethral hyperthermia devices. Five years later, after rigorous testing, the Prostatron device, manufactured by Urologix, received final FDA approval. Another device, Targis, produced by the same manufacturer, is also FDA approved for the treatment of BPH. Both devices deliver relatively high energy (60 watts and more) and feature a water-cooling balloon to lower the temperature in the prostatic urethra.

A third high-energy device, CoreTherm which features an intraprostatic temperature feedback mechanism but no water cooling, was FDA approved in December of 2002 based on the results of a TURP-controlled, randomized trial[59]. The device produced symptom, flow rate, and urodynamic parameter improvement comparable to TURP. An indwelling catheter was maintained in all patients treated with CoreTherm for 14 days (compared to 3 days in the TURP-treated group) and 19% had urinary retention during the 12-month follow-up. Prolonged

catheterization may have been necessary in patients who were treated with the CoreTherm device because urethral necrosis and sloughing occur in the absence of water cooling.

Modeled after BSD Medical's (Salt Lake City, Utah) hyperthermia device, TherMatrx delivers lower energy (7 watts) and features no water cooling. In a sham-controlled trial with a 2:1 randomization in 200 patients [66, 60], TherMatrx demonstrated superior symptom relief compared to the sham-treated group, but after a 3-month follow-up, no differences were found in flow-rate improvement between the active treatment group and the sham-treated patients[67].

In the average patient, transurethral microwave heat treatment is more effective than medical therapy but less effective than surgery in relieving symptoms. Controlled trials of up to 6 months duration suggest superiority of transurethral microwave heat treatment over sham treatment. Irritative voiding symptoms can persist for weeks, and temporary urinary retention is a common risk.

> **Standard: Because unexpected procedure-related injuries have been associated with the use of transurethral microwave heat treatment devices, the following safety recommendations published by the United States Food and Drug Administration [68] should be followed when using microwave heat treatment devices. [The following bolded text was taken directly from the FDA notice.]**
>
> - **When considering a patient for microwave thermotherapy for BPH, ensure that he meets the device's indications, including the criteria for eligible prostate size indicated for the specific system being used. Additionally, it is important to verify that the patient has not had prior radiation therapy to the pelvic area, as these patients are at increased risk of rectal fistula formation. Furthermore, the labeling of each device lists specific patient populations for which safety and effectiveness of this therapy are unknown (e.g., those with prostate cancer).**
> - **When discussing the procedure with the patient, it is important to ensure that he understands the risks and benefits listed in the labeling of the specific device. He**

also should understand the duration of the procedure, the level of pain or discomfort that should be considered normal, the importance of telling the physician of any unusual pain during treatment, how to operate any emergency stop button, and the need to remain as still as possible during treatment.

- **Carefully follow the instructions for use provided with these microwave systems. Note that they require the physician to continually supervise the procedure throughout the entire treatment period. The physician must (1) verify that the retention balloons of the urethral catheter and rectal temperature sensor probe are free of leaks and (2) confirm the placement of the urethral catheter and rectal temperature sensor using acceptable methods (e.g., direct visualization, ultrasound imaging) both prior to treatment and at other specified times consistent with the manufacturer's recommendations. Either patient movement or component breakage may cause migration of a properly placed urethral catheter or rectal temperature sensor.**
- **Be careful not to oversedate the patient. As patient perception of pain is an important safety mechanism to ensure that the heating of the tissue is not excessive. General or spinal anesthesia should not be used.**
- **Closely monitor the patient and the equipment throughout the entire treatment, and manually pause treatment if the patient complains of excessive pain or anything unusual occurs.**

While the Panel agrees in principle with the safety recommendations published by the FDA, it recognizes that these procedures can be safely performed under general or spinal anesthesia provided that all other safety measures are taken such as verifying position of the treatment catheter and retention balloon.

Transurethral needle ablation

Option: Transurethral needle ablation (TUNA) is effective treatment in partially relieving symptoms of BPH.

For the relief of symptoms in the average patient, TUNA appears to be more effective than medical therapy but less effective than TURP. Common risks include irritative urinary symptoms that can persist for weeks and temporary urinary retention. The efficacy of TUNA appears to be

similar to that achieved by the TUMT devices. However, in general, it appears that TUNA has a higher requirement for analgesia/sedation/anesthesia than does TUMT.

Transurethral needle ablation uses RF waves (490 KHz) to heat prostatic tissue. The RF energy is administered through two 18-gauge needles at the tip of a TUNA catheter. This catheter resembles a rigid cystoscope and contains a lens that guides placement in the urethra using direct vision. The needles are advanced into the prostate parenchyma by piercing the urethra. Tissue in the lateral prostatic lobes is heated to about 100^{o}C to produce coagulation necrosis. Both needles have insulating sheaths to protect the urethral mucosa from heating. The ideal patient for this procedure is a man who has obstructive BPH, a prostate of 60 g or less, and predominantly lateral lobe enlargement [69, 70].

Stents

Guideline: Because prostatic stents are associated with significant complications, such as encrustation, infection and chronic pain, their placement should be considered only in high-risk patients, especially those with urinary retention.

Prostatic stents are metal (or polyurethane) devices that can be placed into the prostatic urethra under either endoscopic or fluoroscopic control. Currently, there is only one stent (metallic) available in the United States. When expanded into the prostatic urethra, they partially relieve the obstruction from the surrounding prostatic tissue. Over a period of a few weeks to a few months, the stents are covered with normal transitional cell epithelium. To date, most BPH patients treated with prostatic stents have been in urinary retention or are too ill for other treatments. A majority of patients have been able to void successfully after placement of the stent [71-73].

Adverse events, such as encrustation (calcification), occlusive regrowth of the stents, as well as some degree of perineal pain and discomfort on urination, have been reported. Clinical trials of temporary prostatic stents are ongoing, and some long-term efficacy and safety studies have been published [74]. It is unclear whether prostatic stents have applications in men with symptomatic BPH who have not developed urinary retention [75] and whose medical conditions permit other forms of treatment [76, 77, 73, 78]. [This recommendation is based on both evidence and Panel expert opinion.]

Surgery

Guideline: The patient may appropriately select surgical treatment as his initial treatment if he has bothersome symptoms. Patients who have developed complications of BPH are best treated surgically.

Option: The choices of surgical approach (open or endoscopic and energy source—electrocautery versus laser) are technical decisions based on the patient's prostate size, the individual surgeon's judgment, and the patient's comorbidities.

Surgical intervention is an appropriate treatment option for patients with moderate-to-severe LUTS and for patients who have developed acute urinary retention or other BPH-related complications. Generally, patients will have tried medical therapy before proceeding with surgery. Medical therapy, though, should not be viewed as a requirement because some patients may wish to have the most effective therapy initially if their symptoms are particularly bothersome. As with other treatment options, the decision to elect surgery as the treatment option should be based upon the patient's own views of treatment risks versus benefits.

The Panel does not believe that it is necessary to offer the patient all subtypes of surgical therapy. The selection of energy source and instrumentation should be based upon the surgeon's experience as well as the patient's individual prostatic anatomy and medical comorbidities.

Despite the development of new technologies in the surgical area, the Panel still views TURP as the benchmark for surgical therapies because of the published evidence of efficacy from randomized clinical trials with long-term follow-up. In general, new surgical technologies have not demonstrated better outcomes than TURP in comparative trials published to date. [These recommendations are expanded from the 1994 AHCPR guideline and are based on evidence and Panel expert opinion.]

Transurethral resection of the prostate

Transurethral resection of the prostate involves the surgical removal of the prostate's inner portion via an endoscopic approach through the urethra, with no external skin incision. An electrified loop is used to resect the prostatic tissue and to cauterize bleeders. This procedure is the most common active treatment for symptomatic BPH. The most definitive published study of TURP, the Veterans Affairs Cooperative Study [30], demonstrates a 1% risk of urinary incontinence (with a similar incidence in the watchful waiting group) and an overall decline in sexual function that was identical to the watchful waiting treatment group. Because of more aggressive PSA-based prostate cancer detection efforts, the tissue analysis provided by TURP is no longer considered an advantage to this technique. Usually performed under general or spinal anesthesia, TURP requires a hospital stay. One unique complication of TURP is TURP syndrome, a dilutional hyponatremia that occurs when irrigant solution is absorbed into the bloodstream. Other complications that have been reported in more than 5% of patients include, in order of frequency: sexual dysfunction (which may not be attributable to the surgery in all cases), irritative voiding symptoms, bladder neck contracture, the need for blood transfusion, UTI, and hematuria.

Transurethral electrovaporization of the prostate

Transurethral electrovaporization is a new procedure that adapts an old device, the roller ball electrode. As described by Kaplan and Te [79], the roller ball is put in a resectoscope and, using a technique similar to a standard TURP, the ball is rolled over the BPH tissue, with the cutting current set up to significantly higher wattage than a standard TURP. With multiple passes, the tissue is vaporized to the desired depth in about the same amount of time required for TURP. Another variant of this procedure, which uses laser energy to vaporize the prostate adenomatous tissue, is discussed below. Compared to TURP, transurethral electrovaporization results in equivalent, short-term improvements in symptom scores, urinary flow rate, and quality-of-life indices. However, the rates of postoperative irritative voiding symptoms, dysuria and urinary retention, as well as the need for unplanned secondary catheterization, appear to be higher. Long-term comparative trials are needed to determine if the transurethral electrovaporization approach is superior to standard TURP.

Transurethral incision of the prostate

Transurethral incision of the prostate is an outpatient endoscopic surgical procedure limited to the treatment of smaller prostates (30 g of resected weight or less). In the TUIP procedure, one or two cuts are made in the prostate and prostate capsule with a Collings knife, reducing constriction of the urethra. In the appropriate patient, TUIP results in degrees of symptomatic improvement equivalent to those attained after TURP [80-83]. In addition, compared to TURP, TUIP results in a significantly reduced risk of retrograde ejaculation. TUIP also was associated with a slightly higher rate of secondary procedures.

Laser therapy

Laser energy has been utilized to destroy neoplastic tissue in a variety of organ systems. In general, laser energy can be used to produce coagulation necrosis, vaporization of tissue, or

resection of tissue, procedures performed on the prostate commonly referred to as transurethral laser coagulation, transurethral laser vaporization, and transurethral holmium laser resection/enucleation, respectively. Initial experiences with bare laser fibers using neodynium:yttrium-aluminum-garnet (Nd:YAG) laser technology have been disappointing, primarily because of their inability to penetrate deeply into the tissue. The first major advance was the development of right-angle laser fibers, which permitted delivery of the energy at right angles to the fiber. Right-angle YAG fibers can be guided under direct vision through a cystoscope or by transurethral ultrasound imaging. Investigators do not agree on the optimal technique of energy delivery. Some of the laser technologies produce coagulation necrosis with delayed slough of tissue. Other lasers result in immediate tissue vaporization and ablation. The holmium laser has demonstrated effectiveness equivalent to TURP but is a procedure that has a considerable learning curve.

Transurethral laser coagulation

During transurethral laser coagulation (visual laser ablation of the prostate [VLAP]), the tip of a right-angle fiber, held approximately 2 mm away from the prostate tissue, is used to deliver laser energy from a transurethral approach. Because the fiber is not in direct contact with the tissue, the procedure is considered to be of low-power density, with energy to coagulate but not to vaporize the tissue. The coagulated tissue eventually necroses and sloughs, relieving the obstruction. The main advantages of this procedure include its technical simplicity, low rates of bleeding and water absorption. Although a large body of evidence describing the outcomes of this surgical technique has been published, the evidence is difficult to summarize statistically because investigators have had varying approaches to this intervention. For example, a standard energy level (usually 60 watts), speed of dragging the fiber over the prostate and number of

treatments per patient (often four quadrants, sometimes more) are not used consistently across studies.

Transurethral laser coagulation of the prostate is an effective surgical treatment for men with BPH. Although improvements in symptom scores, quality-of-life indices, and flow rate are equivalent to those attained after TURP, significantly higher rates of unplanned, prolonged, postoperative urinary catheterization and a higher incidence of postprocedure irritative voiding symptoms are reported. The Panel's meta-analysis found that the rate of acute urinary retention requiring secondary catheterization posttransurethral laser coagulation was 21% in the single-arm analysis, significantly higher than that observed post-TURP (5%, single-arm analysis only). The rate of postprocedure irritative voiding symptoms observed after transurethral laser coagulation in the meta-analysis of two randomized, direct comparison trials was not significantly different from the rate (15%) observed after TURP. However, the single-arm rate of irritative voiding symptoms after laser coagulation (66%) appears significantly higher than the 15% rate observed after TURP. The reason for this variation is not clear.

Transurethral laser vaporization

In a technique similar to transurethral electrovaporization with electrocautery, the prostate tissue also can be vaporized using laser energy. The laser fiber is maintained in contact (in contrast to the coagulation procedure during which the fiber is kept at a distance from the tissue) with the area to be treated and a series of furrows is made until a wide channel is obtained. Like transurethral electrovaporization, laser vaporization of the prostate results in equivalent short-term improvements in symptom scores, urinary flow rate, and quality-of-life indices when compared to TURP. In addition, the rates of postoperative urinary retention and the need for

unplanned secondary catheterization reported with laser vaporization also appear to be higher than for TURP.

Transurethral holmium laser resection/enucleation

Transurethral holmium laser resection/enucleation is a relatively new technique in which the prostatic adenoma is resected using a holmium laser fiber and a specially adapted resectoscope [84]. Data suggest that the intermediate-term, symptomatic improvement obtained after holmium laser resection may be comparable to that obtained after TURP, with a slightly reduced risk of bleeding and need for blood transfusions and an absence of TURP syndrome [85].

The holmium laser also has been applied to the treatment of very large glands in the form of a laser enucleation with subsequent intravesical tissue morcellation. The results compare favorably to open prostatectomy in the hands of an experienced surgeon [86-88]. In other trials, improvements in symptom scores, quality-of-life indices, and flow rate, in some series, approach those obtained after TURP [89, 90]. Nonetheless, long-term data beyond 2 years are still lacking [89], and the procedure requires specialized training and equipment. For these reasons, TURP remains the procedure of choice for patients who elect or require surgery for BPH. In medical centers where the procedure is available, transurethral holmium laser resection is an option for patients seeking an alternative method of resection/enucleation.

Open prostatectomy

Open prostatectomy involves the surgical removal (enucleation) of the inner portion of the prostate via a suprapubic or retropubic incision in the lower abdominal area. This procedure is also rarely performed through the perineum. Open prostatectomy typically is performed on patients with prostate volumes greater than 80 to 100 mL [2].

Emerging Therapies

The Panel examined data on a number of emerging therapies that are listed in Table 1.2.

Table 1.2. Emerging therapies

Phytotherapeutic agents
Absolute ethanol injection
High-intensity focused ultrasound
Transurethral heat-based therapies
Interstitial laser coagulation
Water-induced thermal therapy
PlasmaKinetic™ Tissue Management System

Guideline: Phytotherapeutic agents and other dietary supplements cannot be recommended for treatment of BPH at this time. [This recommendation is based on both evidence and Panel expert opinion.]

Guideline: The Panel believes that additional data are required before the following therapies can be considered as recommended treatment options: interstitial laser coagulation, water-induced thermotherapy, and the PlasmaKinetic™ Tissue Management System. All of these interventions are categorized as emerging therapies even though several are FDA approved either for BPH or soft tissue ablation. It is not inappropriate for these options to be offered to the patient, but the uncertainty of outcomes compared to the recommended treatment options should be discussed with the patient.

Guideline: High-intensity focused ultrasound and absolute ethanol injection are investigational at this time and should not be offered outside the framework of clinical trials.

Phytotherapeutic agents and other dietary supplements are used extensively worldwide for the treatment of LUTS. The most popular agent*, Serenoa repens*, is used either as monotherapy or in multiagent regimens. The disparities in the raw products (plants), variations in extraction procedures, and the lack of identity of the potentially active component all impinge on the ability of the manufacturer to ensure product potency and thus product-to-product consistency. Despite their widespread use, the mechanisms of action, effectiveness, and safety of these agents have

not been well documented in multicenter, randomized, clinical trials with independent data monitoring.

Transurethral injection of absolute ethanol into the prostate results in coagulative necrosis (chemo-ablation). Following a preliminary report from Japan [91], canine studies were performed in the United States [92]; recently, a single-center human experience in 15 patients was reported [93]. A multicenter trial evaluating this technology in patients with BPH currently is under way.

High-intensity focused ultrasound uses timed bursts of ultrasound to create coagulation necrosis in a targeted area of tissue. Frequencies can range as high as 10 MHz depending on the device, heating tissue to 70^{o}C or higher. However, 4 MHz typically is used. The same piezoceramic element used for focal therapy also can be used for ultrasound imaging, which allows incorporation of therapeutic and diagnostic components in the same small rectal probe. High intensity focused ultrasound therapy is still investigational. In a review of HIFU devices and treatment results to date, McCullough [62] described the therapy as "moderately promising" for BPH [54, 94], but additional long-term studies are warranted. Clinical trials are now under way.

Interstitial laser coagulation of the prostate by the transurethral route has been attempted using several laser sources and delivery devices. In the United States (and worldwide), a diode laser device, the Indigo 830e (Ethicon Endo-Surgery, Cincinnati, Ohio), has been evaluated [55, 56]. At present, a multicenter trial is under way using this technology in men with BPH.

Water-induced thermal therapy had been approved by the FDA for the treatment of BPH after a single international, uncontrolled, multicenter trial demonstrated symptom reduction and safety [57]. Since that time an additional favorable single-center experience has been published [58].

Using plasma energy in a saline environment to achieve tissue vaporization with minimal thermal spread and enhanced hemostasis, the PlasmaKinetic Tissue Management System (Gyrus,

Maple Grove, Minnesota) has the potential to increase safety by eliminating potential hyponatremia and TURP syndrome. A positive single-center, short-term experience in 42 patients has been published [95].

Balloon Dilation: Not Recommended

> **Guideline: Balloon dilation is not recommended as a treatment option for patients with symptoms of BPH.**

Balloon dilation involves the insertion of a balloon on a catheter tip through the urethra and into the prostatic urethra. The balloon is then inflated to stretch the urethra where narrowed by the prostate. Balloon dilation has been inadequately studied. Short-term studies in the late 1980s were promising but longer follow-up studies demonstrated a significant failure rate over time. The one published controlled trial suggests that balloon dilation produces minimal improvement compared with cystoscopy [96], but this study is not definitive because of the small number of patients enrolled and the resultant broad confidence intervals surrounding the efficacy estimates. Upon a review of available data, McCullough [62] noted reports of transient improvement, especially in symptom scores, but few accounts of long-term improvement in peak flow rate and PVR volume. Moreover, the number of papers dealing with balloon dilation has been decelerating rapidly, indicating a falloff in enthusiasm for this treatment. The 4th International Consultation on BPH stated in its guidelines that balloon dilation is not an acceptable treatment option [9]. [This recommendation is based on Panel expert opinion.]

Therapies for Patients With Uncommon or Serious Complications of BPH

> **Guideline: Surgery is recommended for patients with refractory retention who have failed at least one attempt at catheter removal. In patients who are not surgical candidates, treatment with intermittent catheterization, an indwelling catheter or stent is recommended.**

Although there are small studies of TUMT and other minimally invasive treatments in men with urinary retention, the Panel felt there were insufficient outcomes data from well-controlled trials to recommend these approaches at the present time. Surgery (as defined in Table 1.1) remains the treatment of choice, assuming the patient's overall health makes him an acceptable risk for the procedure.

> **Option: Concomitant administration of an alpha blocker is an option prior to attempted catheter removal in patients with urinary retention.** [This recommendation is based on Panel expert opinion.]

Using a nontitratable alpha blocker (e.g., tamsulosin or alfuzosin) prior to a trial of catheter removal may be preferable. Concomitant administration of an alpha blocker would not be appropriate, however, in a patient with either a prior history of alpha-blocker side effects or unstable medical comorbidities (e.g., orthostatic hypertension or cerebral vascular disease) that could increase the risks associated with alpha-blocker therapy. Overall, a voiding trial is more likely to be successful if underlying retention is precipitated by temporary factors (e.g., anesthesia or alpha-adrenergic sympathomimetic cold medications) [97].

> **Guideline: Surgery is recommended for patients who have renal insufficiency clearly due to BPH and in those patients with recurrent UTIs, recurrent gross hematuria, or bladder stones clearly due to BPH and refractory to other therapies. The presence of a bladder diverticulum is not an absolute indication for surgery unless it is associated with recurrent UTI or progressive bladder dysfunction.** [This recommendation is based on Panel expert opinion.]

Men who have developed serious complications of BPH should in most cases be treated surgically (as defined in Table 1.1). Both the 1994 AHCPR guideline and the International Consultation on BPH guidelines recommend surgery in the patient with refractory urinary retention (failing at least one attempt of catheter removal) or any of the following conditions,

which are secondary to BPH: bladder stone, recurrent UTI, recurrent gross hematuria, renal insufficiency, or large bladder diverticula.

Bladder stones due to BPH are rare. In a large autopsy study, the incidence of bladder stones was 3.4% in patients with a histological finding of BPH versus 0.4% in controls [98]. Only one of 276 patients with BPH and moderate symptoms developed bladder stones during 3 years of follow-up in a study comparing watchful waiting with TURP [30]. Recently, successful treatment of patients with BPH and bladder calculi was reported by removing the stones surgically and treating the patients medically [99].

Urinary tract infections were found in 12% of men presenting for TURP in older series [100], but in the MTOPS study, only 1% of all progression endpoints were due to the diagnosis of a recurrent UTI over a 5-year follow-up period [51]. A single UTI was reported as an adverse event in 6% of the 182 evaluable patients over a 4- to 5-year follow-up period, or approximately 1.5% annually.

Prostatic bleeding is an uncommon complication of BPH. Gross hematuria must be proven to be of prostatic etiology through appropriate evaluation [101]. A 5 alpha-reductase inhibitor may decrease the probability of prostate bleeding. Medical therapy is contraindicated in patients who have not been adequately evaluated or in patients with microscopic hematuria alone.

Summary

This guideline updates the recommendations of the 1994 AHCPR benign prostatic hyperplasia clinical practice guideline by 1) making minimal modifications to the recommended diagnostic methods for detecting and assessing the severity of BPH, based on expert clinical judgment, and 2) employing explicit, science-based methodology to develop new and to update existing statements on patient management. Extensive literature searches were conducted, and

critical reviews and syntheses were used to evaluate empirical evidence and significant outcomes of all currently available treatment approaches. These processes and findings are detailed in the next two chapters. In Chapter 2, the methods by which the outcomes data were synthesized and the drawbacks of these methods are reviewed. Chapter 3 then details the results of the analyses of clinical management study outcomes data and probability estimates for the potential benefits and complications associated with the treatment of LUTS and clinical BPH.

Since the 1994 AHCPR guideline was written, our knowledge of the natural history and epidemiology of LUTS and BPH has increased rapidly along with a new understanding of the efficacy and safety of medical interventions. This gain is attributable to the conduct of a multitude of well-planned and well-executed clinical trials. Some of the issues raised with the 1994 AHCPR guideline, however, still remain controversial while other concerns and knowledge gaps have arisen. Chapter 4 reviews the need not only for additional information in this therapeutic area but also the need for better reporting and publication standards.

Appendix 1-A: The American Urological Association (AUA) Symptom Index for Benign Prostatic Hyperplasia (BPH) and the Disease Specific Quality of Life Question

Patient Name: _____ DOB: _____ ID: _____ Date of assessment: _____

Initial Assessment ( ) Monitor during: _____ Therapy ( ) after:_____ Therapy/surgery ( ) _____

AUA BPH Symptom Score

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5.Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 or more times	
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
						Total Symptom Score	

The Disease Specific Quality of Life Question

The International Prostate Symptom Score uses the same 7 questions as the AUA Symptom Index (presented above) with the addition of the following Disease Specific Quality of Life Question (bother score) scored on a scale from 0 to 6 points (delighted to terrible):

"If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?"

Appendix 1-B: Benign Prostatic Hyperplasia (BPH) Impact Index

Patient Name:_____DOB:_____ ID:_____ Date of assessment: _____

Initial Assessment ( ) Monitor during:_____ Therapy ( ) after:_____ Therapy/surgery ( )_____

BPH Impact Index

1. Over the past month how much physical discomfort did any urinary problems cause you?	None ☐ Only a little ☐ Some ☐ A lot ☐
2. Over the past month, how much did you worry about your health because of any urinary problems?	None ☐ Only a little ☐ Some ☐ A lot ☐
3. Overall, how bothersome has any trouble with urination been during the past month?	Not at all bothersome ☐ Bothers me some ☐ Bothers me a little ☐ Bothers me a lot ☐
4. Over the past month, how much of the time has any urinary problem kept you from doing the kind of things you would usually do?	None of the time ☐ Most of the time ☐ A little of the time ☐ All of the time ☐ Some of the time ☐
	Total Score: (Scoring based on 0-4 point scale)

Appendix 1-C: Simplified Outcomes Tables

Table 1-C-a. Outcomes of medical therapies: estimates of change in efficacy scores/rates

	AUA / IPSS			Peak Flow Rate (Qmax)			QoL Question Score		BPH Impact Index	
	3-9 Months	10-16 Months	>16 Months	3-9 Months	10-16 Months	>16 Months	3-9 Months	10-16 Months	3-9 Months	10-16 Months
Alpha Blockers										
Alfuzosin	-4.44			2.05			-1.10			
Doxazosin	-5.10	-5.63		3.11	2.98	1.90*	-1.25	-1.47	-2.00	-2.47
Tamsulosin	-4.63	-7.53*		1.85	1.86*		-1.43			
Terazosin	-6.22	-5.99		2.51	1.94	2.61*	-1.70*	-1.37	-1.45*	-2.09
Hormonal										
Finasteride	-3.44	-3.40	-2.37	2.11	1.66	1.95	-0.75	-0.87	-1.50	-1.21
Combinations										
Alfuzosin/Finasteride	-6.10*			2.30*						
Doxazosin/Finasteride	-5.64	-6.53		3.96	3.38		-1.15	-1.57	-2.20	-2.57
Terazosin/Finasteride	-5.90*	-6.21*		3.50*	2.63				-1.55*	-2.03
Placebo	-2.44*	-2.33*	-1.03*	0.86*	0.48*	0.48*	-0.65*	-0.67*	-1.00*	-0.97*

*These numbers are based on single-arm analyses — no RCT data available.
Numbers without asterisks are based on RCT results with placebo controls.

Appendix 1-C: Simplified Outcomes Tables

Table 1-C-b. Outcomes of minimally invasive therapies: estimates of change in efficacy scores/rates

	AUA / IPSS			Peak Flow Rate (Qmax)			QoL Question Score			BPH Impact Index	
	3-9 Months	10-16 Months	>16 Months	3-9 Months	10-16 Months	>16 Months	3-9 Months	10-16 Months	>16 Months	3-9 Months	10-16 Months
UroLume Stent	-11.15 *	-12.44 *	-13.22 *	7.37 *	7.80 *						
Thermal-based therapies											
Prostatron Version 2.0 TUMT	-10.93 *	-10.47 *	-9.27 *	3.39 *	2.81 *	2.26 *	-1.95 *	-1.75 *	-1.70 *		
Prostatron Version 2.5 TUMT	-8.83 *	-10.72 *	-10.73 *	4.51 *	4.54 *	4.42 *	-1.25 *				
Targis TUMT	-10.14 ***	-9.44	-10.76 *	2.64 ***	5.29	3.28 *	-2.20 ***	-2.44	-2.31 *		
TUNA	-11.48	-9.32	-8.10	3.01	4.25	-0.93	-3.06	-2.70	-2.44	-5.20 *	-5.00 *
Watchful Waiting	-1.00 *	-0.50 *		-0.03 *		2.16					
Sham (control)	-6.37 *			1.03 *			-1.04 *			-2.30 *	
TURP (control)	-14.65 *	-14.80 *	-13.54 *	10.54 *	10.77 *	8.06 *	-3.44 *	-3.34 *	-3.03 *		

*These numbers are based on single-arm analyses — no RCT data available. Note that single-arm analyses are the same for TURP comparisons.

**Single-arm numbers used here because the RCT results were deemed unreasonable due most likely to technique, patient selection or other problems.

***RCT comparison to sham.

Cells without asterisks are RCT comparisons to TURP.

Appendix 1-C: Simplified Outcomes Tables

Table 1-C-c. Outcomes of surgical therapies: estimates of change in efficacy scores/rates

	AUA / IPSS			Peak Flow Rate (Qmax)			QoL Question Score			BPH Impact Index	
	3-9 Months	10-16 Months	>16 Months	3-9 Months	10-16 Months	>16 Months	3-9 Months	10-16 Months	>16 Months	3-9 Months	10-16 Months
TURP	-14.65*	-14.80*	-13.54*	10.54*	10.77*	8.06*	-3.44*	-3.34*	-3.03*		
Holmium Laser Resection/Enucleation	-17.77*	-17.90*		12.16*	10.96*						
Transurethral Laser Coagulation	-16.96	-20.20	-18.44	8.49	10.97	3.26	-3.22*				
TUIP	-11.86*	-15.19	-10.79*	8.66*	7.65**	6.31*		-3.67*	-3.73*		
Transurethral Electrovaporization	-11.49*	-15.75*	-19.34*	10.51*	12.52*	12.46*	-3.60*	-3.70*			
Transurethral Laser Vaporization	-13.43*	-14.10*	-14.20*	6.64	11.10*	9.00*	-4.02*	-1.70*			
Open Prostatectomy			-10.11*	15.50*	11.50*	14.01*					
Watchful Waiting	-1.00*	-0.50*		-0.03*		2.16					

**These numbers are based on single-arm analyses — no RCT data available. Note that single-arm analyses are the same for TURP comparisons.*

***Single-arm numbers used here because the RCT results were deemed unreasonable due most likely to technique, patient selection or other problems.*

Numbers without asterisks are based on RCT results with TURP controls.

Appendix 1-C: Simplified Outcomes Tables

Table 1-C-d. Outcomes of medical therapies: estimates of occurrence of adverse events

	Median (95% CI)								
	Acute Urinary Retention	Asthenia	Breast	Cardiovascular	Cardiovascular-Peripheral Edema	Cardiovascular-Serious	Dizziness	GI Systems	Headache
Alpha Blockers									
Alfuzosin		4% (1-10)		1% (0 - 4)	0% (0 - 1)		5% (1 - 12)	10% (6 - 15)	5% (3 - 9)
Doxazosin	0% (0 - 1)	15% (13 - 18)		2% (1 - 4)	1% (1 - 3)		13% (9 - 19)	10% (6 - 15)	8% (4 - 12)
Tamsulosin	4% (1 - 8)	7% (3 - 12)		8% (2 - 18)			12% (8 - 17)	11% (6 – 18)	12% (6 – 19)
Terazosin	4% (1 - 8)	12% (10 - 13)		2% (1 - 3)	4% (2 - 6)	0% (0 - 0)	15% (12 - 20)	5% (3 - 9)	7% (5 – 10)
Hormonal									
Finasteride	2% (1 - 2)	2% (1 - 4)	1% (0 - 2)	5% (2 - 10)		1% (0 - 3)	5% (2 - 10)	6% (3 – 10)	4% (2 - 6)
Combination									
Alfuzosin/finasteride	0% (0 - 1)	1% (0 - 2)				0% (0 - 1)	2% (1 - 4)		2% (1 - 3)
Doxazosin/finasteride	0% (0 - 1)	13% (9 - 17)		2% (1 - 4)			14% (11 - 19)	8% (6 - 12)	9% (6 – 13)
Terazosin/finasteride		14% (11 - 18)					21% (17 - 26)		5% (3 - 8)
Placebo	3% (2 - 5)	4% (3 - 5)	2% (0 - 5)	4% (2 - 7)	1% (1 - 2)	1% (1 - 1)	5% (4 - 7)	6% (4 - 9)	5% (4 - 7)

Appendix 1-C: Simplified Outcomes Tables

Table 1-C-d. Outcomes of medical therapies: estimates of occurrence of adverse events (continued)

	Median (95% CI)							
	Hypotension-Asymptomatic	Hypotension-Symptomatic	Hypotension-Symptomatic Postural	Hypotension-Symptomatic Syncope	Respiratory-Nasal Congestion	Sexual-Ejaculation	Sexual-Erectile Problems	Sexual-Libido
Alpha Blockers								
Alfuzosin		1% (0 - 3)		1% (0 - 3)	6% (1 - 15)		3% (1 - 6)	1% (0 - 4)
Doxazosin	5% (3 - 10)		4% (1 - 9)	0% (0 - 2)	8% (1 - 25)	0% (0 - 2)	4% (1 - 8)	3% (2 - 6)
Tamsulosin	7% (2 - 15)		3% (1 - 6)	1% (0 - 1)	11% (4 - 23)	10% (6 - 15)	4% (1 - 8)	
Terazosin	8% (2 - 18)	3% (1 - 8)	6% (3 - 11)	1% (1 - 3)	6% (4 - 10)	1% (1 - 2)	5% (3 - 8)	3% (1 - 5)
Hormonal								
Finasteride	4% (1 - 12)		2% (1 - 3)	1% (0 - 3)	9% (2 - 22)	4% (3 - 5)	8% (6 - 11)	5% (4 - 7)
Combination								
Alfuzosin/finasteride	8% (6 - 11)		1% (0 - 2)			1% (0 - 2)	8% (5 - 11)	2% (1 - 4)
Doxazosin/finasteride	3% (1 - 5)		3% (1 - 5)	2% (1 - 3)	18% (14 - 23)	3% (2 - 6)	10% (7 - 14)	3% (1 - 5)
Terazosin/finasteride			9% (6 - 12)	2% (1 - 4)	10% (7 - 14)	7% (5 - 10)	9% (1 - 13)	5% (3 - 8)
Placebo	2% (1 - 3)	2% (0 - 5)	1% (1 - 2)	1% (0 - 1)	6% (3 - 10)	1% (1 - 1)	4% (3 - 5)	3% (3 - 4)

Appendix 1-C: Simplified Outcomes Tables

Table 1-C-e. Outcomes of minimally invasive therapies: estimates of rates of occurrence of adverse events

	Median (95% CI)							
	Aborted Procedure/ Device Failure	Acute Urinary Retention	BNC/Stricture	Cardiovascular	Cardiovascular-Serious	Cardiovascular-Thromboembolic	Hematuria-Significant	Incontinence
UroLume Stent	34% (11 - 64)	6% (2 - 15)					6% (2 - 14)	25% (7 - 53)
Thermal-based therapies								
Prostatron Version 2.0 TUMT	1% (0 - 3)	23% (18 - 29)	1% (0 - 2)				2% (1 - 4)	2% (1 - 4)
Prostatron Version 2.5 TUMT		15% (4 - 33)	2% (0 - 9)					
Targis TUMT	1% (0 - 4)	6% (1 - 17)	3% (1 - 6)					
TUNA	4% (1 - 9)	20% (13 - 29)	3% (1 - 6)			2% (0 - 6)	4% (1 - 9)	1% (0 - 4)
Watchful Waiting		3% (2 - 6)				0% (0 - 1)		2% (1 - 3)
Sham (control)	1% (0 - 6)	3% (1 - 5)	1% (0 - 6)	0% (0 – 3)				1% (0 - 6)
TURP (control)		5% (4 - 8)	7% (5 - 8)	1% (0 – 2)	2% (0 - 6)	2% (0 - 8)	6% (5 - 8)	3% (2 - 5)

Appendix 1-C: Simplified Outcomes Tables

Table 1-C-e. Outcomes of minimally invasive therapies: estimates of rates of occurrence of adverse events (continued)

	Median (95% CI)						
	Infection/UTI	Intraoperative	Post-procedure Irritative	Secondary Procedure	Sexual-Ejaculation	Sexual-Erectile Problems	Transfusion
UroLume Stent	11% (6 - 18)		92% (75 - 99)	10% (5 - 19)			
Thermal-based therapies							
Prostatron Version 2.0 TUMT	9% (5 - 15)		28% (12 - 48)	10% (6 - 16)	5% (4 - 8)	3% (1 - 5)	1% (0 - 4)
Prostatron Version 2.5 TUMT	9% (3 - 19)		74% (18 - 99)	10% (5 - 18)	16% (2 - 49)	1% (0 - 8)	2% (0 - 9)
Targis TUMT	9% (5 - 15)	3% (1 - 6)		16% (11 - 20)	5% (2 - 10)		0% (0 - 2)
TUNA	17% (9 - 29)	11% (1 - 38)	31% (11 - 58)	23% (15 - 34)	4% (1 - 10)	3% (1 - 6)	3% (1 - 8)
Watchful Waiting	0% (0 - 1)	0% (0 - 1)		55% (49 - 61)		21% (17 - 26)	0% (0 - 1)
Sham (control)	5% (2 - 11)	1% (0 - 6)	70% (10 - 99)	24% (10 - 42)	2% (0 - 5)	2% (1 - 6)	1% (0 - 6)
TURP (control)	6% (5 - 9)	3% (3 - 4)	15% (9 - 23)	5% (4 - 6)	65% (56 - 72)	10% (7 - 13)	8% (5 - 11)

Appendix 1-C: Simplified Outcomes Tables

Table 1-C-f. Outcomes of surgical therapies: estimates of occurrence of adverse events

	Median (95% CI)							
	Aborted Procedure/ Device Failure	Acute Urinary Retention	BNC/Stricture	Cardiovascular	Cardiovascular-Serious	Cardiovascular-Thromboembolic	Hematuria-Significant	Incontinence
TURP		5% (4 - 8)	7% (5 - 8)	1% (0 - 2)	2% (0 - 6)	2% (0 - 8)	6% (5 - 8)	3% (2 - 5)
Holmium Laser Resection/Enucleation		8% (2 - 17)	5% (1 - 19)				3% (1 - 9)	1% (0 - 11)
Transurethral Laser Coagulation		21% (16 - 28)	5% (3 - 7)		2% (0 - 6)	2% (0 - 6)	3% (1 - 6)	1% (0 - 3)
TUIP		6% (3 - 10)	6% (4 - 10)				5% (1 - 15)	2% (1 - 6)
TURP - Electrovaporization		12% (7 - 17)	5% (4 - 8)				6% (3 - 9)	3% (2 - 6)
Transurethral Laser Vaporization		13% (8 - 19)	3% (1 - 6)				10% (4 - 20)	3% (1 - 6)
Open Prostatectomy		1% (0 - 8)	8% (2 - 17)			1% (0 - 3)	1% (0 - 8)	6% (1 - 20)
Watchful Waiting		3% (2 - 6)				0% (0 - 1)		2% (1 - 3)

Appendix 1-C: Simplified Outcomes Tables

Table 1-C-f. Outcomes of surgical therapies: estimates of occurrence of adverse events (continued)

	Median (95% CI)						
	Infection/UTI	Intraoperative	Post-Procedure Irritative	Secondary Procedure	Sexual-Ejaculation	Sexual-Erectile Problems	Transfusion
TURP	6% (5 - 9)	3% (3 - 4)	15% (9 - 23)	5% (4 - 6)	65% (56 - 72)	10% (7 - 13)	8% (5 - 11)
Holmium Laser Resection/Enucleation	1% (0 - 11)		6% (2 - 13)	1% (1 - 11)	59% (37 - 79)	3% (0 - 12)	2% (0 - 7)
Transurethral Laser Coagulation	9% (6 - 13)	3% (1 - 9)	66% (44 - 84)	7% (5 - 9)	17% (12 - 24)	6% (3 - 12)	2% (1 - 4)
TUIP	5% (3 - 8)	2% (0 - 6)	99% (96 - 100)	14% (8 - 22)	18% (12 - 25)	13% (6 - 23)	3% (1 - 7)
TURP - Electrovaporization	8% (4 - 15)	3% (1 - 9)	23% (12 - 38)	8% (5 - 11)	65% (43 - 83)	8% (4 - 12)	1% (1 - 3)
Transurethral Laser Vaporization	9% (6 - 12)	3% (1 - 7)	36% (25 - 49)	8% (5 - 11)	42% (21 - 66)	7% (4 - 11)	3% (1 - 5)
Open Prostatectomy	8% (3 - 17)			1% (0 - 8)	61% (35 - 84)		27% (23 - 32)
Watchful Waiting	0% (0 - 1)	0% (0 - 1)		55% (49 - 61)		21% (17 - 26)	0% (0 - 1)