European Association of Urology

# GUIDELINES ON BENIGN PROSTATIC HYPERPLASIA

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# 1. BACKGROUND

Benign prostatic hyperplasia (BPH) is a condition intimately related to ageing (1). Although it is not life-threatening, its clinical manifestation as lower urinary tract symptoms (LUTS) reduces the patient's quality of life (2). Troublesome LUTS can occur in up to 30% of men older than 65 years (3).

## 1.1 Prevalence

Although many epidemiological clinical studies have been conducted worldwide over the last 20 years, the prevalence of clinical BPH remains difficult to determine. A standardized clinical definition of BPH is lacking, which makes it intrinsically difficult to perform adequate epidemiological studies. Among the published epidemiological studies, some include probability samples from an entire country, while others represent age-stratified random samples or enrol participants from general practice, hospital populations or responders to selective screening programmes. There is also a lack of homogeneity among these studies in the way in which BPH is assessed, with different questionnaires and methods of administration.

Barry et al. have provided the histological prevalence of BPH, based on a review of five studies relating age to histological findings in human male prostate glands (4). Histological BPH was not found in men under the age of 30 years but its incidence rose with age, reaching a peak in the ninth decade. At that age, BPH was found in 88% of histological samples (4). A palpable enlargement of the prostate has been found in up to 20% of males in their 60s and in 43% in their 80's (5); however, prostate enlargement is not always related to clinical symptoms (2).

Clinical BPH is a highly prevalent disease. By the age of 60 years, nearly 60% of the cohort of the Baltimore Longitudinal Study of Aging had some degree of clinical BPH (6). In the USA, results of the Olmstead County survey, in a sample of unselected Caucasian men aged 40-79 years, showed that moderate-to-severe symptoms can occur among 13% of men aged 40-49 years and among 28% of those older than 70 years (1). In Canada, 23% of the cohort studied presented with moderate-to-severe symptoms (7). The findings for prevalence of LUTS in Europe are similar to those in the USA. In Scotland and in the area of Maastricht, the Netherlands, the prevalence of symptoms increased from 14% of men in their 40's to 43% in their 60's (8,9). Depending on the sample, the prevalence of moderate-to-severe symptoms varies from 14% in France to 30% in the Netherlands (10,11). The proportion of men with moderate-to-severe symptoms doubles with each decade of life (10). Preliminary results of one of the most recent European epidemiological studies on the prevalence of LUTS show that approximately 30% of German males aged 50-80 years present with moderate-to-severe symptoms according to the International Prostate Symptom Score (i.e. I-PSS >7) (12).

A multicentre study performed in different countries in Asia showed that the age-specific percentages of men with moderate-to-severe symptoms were higher than those in America (13,14). The prevalence increases from 18% for men in their 40s to 56% for those in their 70s (13). Curiously, the average weight of Japanese glands seemed to be smaller than those of their American counterparts (15). Despite methodological differences, some conclusions can be drawn from the studies mentioned above:

- Mild urinary symptoms are very common among men aged 50 years and older.
- Mild symptoms are associated with little bother, while moderate and severe symptoms are associated with increasingly higher levels of inconvenience and interference with living activities (16).
- The same symptoms can cause different troublesome and daily living interference (17).
- The correlation between symptoms, prostate size and urinary flow rate is relatively low (18).

It must be stressed that there is still a need for an epidemiological definition of BPH and its true incidence has yet to be determined (19).

## 1.2 Natural history

Few studies have been carried out on the natural history of BPH. The fact that the projected 10-year risk of developing acute retention varies between 4% and 73% in different studies highlights the uncertainty concerning the course of untreated BPH (20). Recently, the 4-year follow-up of the Proscar long-term efficacy and safety study (PLESS) provided an ultimate 6.6% rate of acute urinary retention for patients treated with placebo (21).

Although there is considerable variation, the long-term follow-up of two well-designed, similar studies (in Scotland and Olmstead County, USA) indicates that the trend for untreated BPH is a slow, but measurable, progression in the severity of urinary symptoms. There is an average increase of approximately 0.18 points per year of follow-up (22), and symptoms are more bothersome at baseline, although their interference with selected life activities increases only slightly (23).

The outcome of clinically diagnosed BPH depends largely on the initial severity of the symptoms. Once the risk of prostate surgery has been evaluated, the results of at least three recent studies should be considered:

1. The Veterans Administration Cooperative Studies programme on clinical trials compared the approach

of watchful waiting (WW) with transurethral resection of the prostate (TURP) in patients younger than 55 years. Three-year follow-up was completed in 94% of men assigned to WW. During this period, 17% of them had a treatment failure,These patients presented with higher symptom scores at baseline (24).

2. The Shared Decision-making Program developed by the Patient Outcome Research Team for Prostate Diseases recruited subjects, who viewed a computer and videodisk (an interactive educational programme) for men facing a treatment decision. The choice between WW and surgery was offered. In November 1993, 810 men had completed baseline evaluation using the program. Forty-three per cent of the men were aged < 65 years and 28% were aged > 70 years. The 1-year outcome data for 612 men showed that surgery was eventually performed in 6% of men with scores in the mild range, 18% of men with scores in the moderate range, and 34% of men with severe scores at baseline (25).
3. Barry *et al*. followed the rate of prostatectomy in a group of 500 candidates for elective prostatectomy for 4 years. At baseline, 10% had mild symptoms, and 24% and 39% had moderate and severe symptoms, respectively. At the end of the follow-up, 63%, 45%, and 33% of patients with mild, moderate or severe symptoms at baseline, respectively, remained without any kind of treatment (26).

# 2. RISK FACTORS

## 2.1 For developing the disease

The aetiology of BPH is multifactorial. Currently, there is no strong evidence that smoking, vasectomy, obesity or high alcohol intake are risk factors in the development of clinical BPH. Results of the different epidemiological studies are controversial, probably because of differences in sampling and methods of analysis. In most cases only insufficient marginal differences can be established (19).

Chronic conditions, such as hypertension or diabetes, have been related to clinical BPH, but given the frequent occurrence of these conditions in ageing men a large proportion of patients can be expected to suffer from such an association (27,28).

Recently, it has been stated that diabetes and clinical BPH are associated more frequently than would be expected based on chance alone. Although more severe BPH symptoms (increased I-PSS and post-void residual) seem to be found in diabetic males even after age adjustment, the fact that both conditions increase with age and can cause partially similar voiding symptoms, produces a considerable bias (28).

The only true factors related to the development of the disease are age and hormonal status (29). The crucial role of the testis has been recognized for more than a century and current research has extended into the field of molecular biology (30). Both of these risk factors are currently beyond prevention.

## 2.2 For surgical treatment

Although the number of surgical procedures for BPH has declined in the USA and Europe over the last decade (31), they still represent the second most common major operation in aged men (20). Ultimately, three in 10 men may undergo surgery for this condition (27).

Surgical risk depends on age and the presence of clinical symptoms. In the absence of clinical symptoms, the likelihood of being treated surgically is about 3% (6,32). The need for surgery increases with symptoms and is twice as high in men with a high baseline-symptom score than for those with a low score (24). For men presenting with urinary retention, the cumulative incidence for prostatectomy is 60% at 1 year and 80% at 7 years (33). Multivariate analysis carried out on a sample of 16,219 men, aged at least 40 years, with a mean follow-up of 12 years, showed a positive association with surgery for age, low body mass index, non-smokers, urine pH greater than 5, and a history of kidney X-ray and or tuberculosis, for each of the five clinical urinary symptoms studied (34).

In the Veterans Normative Aging Study, in a cohort of 2,280 men, the main predictor for surgery was the presence of urinary symptoms. The risk of requiring subsequent surgery also varied with age, the odds ratio being 1.8 for nocturia and 4.3 for hesitancy in young men (aged < 65 years). Among older men, only nocturia (odds ratio 2.4) was predictive of surgery (35). In the Baltimore study, the three predictive symptoms for surgery were change in size and force of the urinary stream, sensation of incomplete voiding and digital rectal enlargement of the prostate. Men with one factor had a cumulative incidence of surgery of 9%, those with two factors of 16%, and those with three factors of 37%. Nevertheless, the same study showed that increasing age was the predominant risk factor for surgery (6).

From the above, it can be concluded that the risk of needing surgery for BPH increases with age and with the degree of clinical symptoms at baseline. Nocturia and changes in urinary stream seem to be the most important predictive symptoms.

# 3. DIAGNOSIS

- Diagnostic investigations have been classified as:
- Mandatory: this test should be performed in every patient
- Recommended: there is evidence to support the use of this test
- Optional: this test is done at the discretion of the clinician
- Not recommended: there is no evidence to support the use of this test

## 3.1 Symptom scores

Numerous scores have been constructed to describe and quantify BPH symptoms and/or their impact on quality of life (Table 1) (36). All of them were intended to compare patient status before and after any kind of BPH treatment. Whether or not a questionnaire is valid, depends on the purpose for which it is being used (37). None of the symptom scores already used in BPH have been constructed to select a particular type of treatment.

**Table 1. : BPH symptom scores. Adapted from McConnell *et al.* 1994 (36).**

| **Aspect** | **Occurrence or frequency** | **Disease-specific health-related quality of life (QoL)** | |
|---|---|---|---|
| | | **Impact of individual symptoms** | **Impact (global)** |
| Lower urinary tract symptoms (excluding continence) | I-PSS (7 questions)<br>DAN-PSS-1<br>ICS male<br>Clinical Prostate Score<br>Bladder Outlet Obstruction Number | DAN-PSS-1<br>ICS male<br><br>Symptom Problem Index | I-PSS (1 QoL question)<br>ICS QoL<br>BPH QoL9<br>BPH Impact Index |
| Continence | DAN-PSS-1<br>ICS male<br>BSFI<br>ICS sex<br>BPH QoL9<br>RSSF | DAN-PSS-1n<br>ICS male<br>BSFI<br>ICS sex<br>RSSF | ICS QoL<br><br>BSFI<br>QoL9<br>RSSF |
| Activities of daily living | | | BPH QoL9<br>ICS QoL<br>SF36 |

BPH = benign prostatic hyperplasia; BSFI = Brief Sexual Function Inventory; DAN-PSS-1 = Danish Prostate Symptom Score-1; ICS = International Continence Score; I-PSS = International Prostate Symptom Score; RSSF = Radiumhemmets Scale of Sexual Functioning.

### 3.1.1 I-PSS

Since 1990, the I-PSS has been recommended by the International Consultations on BPH. The I-PSS, constructed on the basis of the American Urological Association (AUA) symptom score, consists of eight questions, seven of which explore urinary symptoms and one, which investigates quality of life. When the I-PSS is greater than 28, the probability of bladder outlet obstruction is more than 0.91%. When the obstructive (or voiding) symptom score (questions 36, 38, 40 and 41) is greater than 15, the probability of bladder outlet obstruction is greater than 0.91% (38). However, in contrast, a patient with a given severity of symptoms cannot be identified as having or not having obstruction through an I-PSS evaluation. Severe bladder outlet obstruction may be found in 15% of patients with minimal symptoms, while no obstruction is found in 25% of patients with severe symptoms (39).

This discrepancy may be partially related to the inability of men to quantify their own clinical status. In a prospective study, the AUA questionnaire was given twice to 42 BPH patients (40). All micturitions during a typical 24-hour period were continuously recorded by a home uroflowmetry system. There was no correlation between daytime frequency, strength and intermittency, and the matching questionnaire answers. Only nocturia

was accurately reported by the questionnaire. No correlation has been found between I-PSS and prostate volume measurement (41). When comparing I-PSS with uroflowmetry and standard pressure-flow study, there was also no relationship between obstruction and I-PSS (42).
It therefore seems impossible to diagnose bladder outlet obstruction from I-PSS alone. Unfortunately, it does not even seem possible to define subgroups in which further urodynamic examination is indicated. Vallancien *et al*. recently proposed a new classification of BPH patients, using the I-PSS (43) system. In this proposed classification (PQSF) (Table 2), which has not yet been validated, four parameters, which are not inter-correlated, are used:

- Prostate weight, P, evaluated by transrectal ultrasound
- Quality of life, Q, evaluated by I-PSS, question no. 8
- Symptoms, S, evaluated by I-PSS
- Maximum flow rate, F, evaluated for a single micturition over 120 mL.

**Table 2. PQSF classification of BPH Adapted from Vallancien et al. (43)**

| **Parameter** | **Stage** | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| P: weight (g) | < 40 | 40-70 | > 70 |
| Q: quality of life | 0-2 | 3, 4 | 5, 6 |
| S: score | < 8 | 8-20 | > 20 |
| F: flow (mL/s) | > 12 | 8-12 | < 8 |

### 3.1.2 Clinical Prostate Score

Rosier *et al*. (44) defined the Clinical Prostate Score, using the most important predictor of bladder outlet obstruction (Table 3). This scoring system is better able to discriminate between patients with or without bladder outlet obstruction. In a study comparing the Clinical Prostate Score and I-PSS in 705 patients, it was shown that when the former was greater than 11 (48.8% of patients with symptomatic BPH evaluated), 80.7% had bladder outlet obstruction (44). When the Clinical Prostate Score was less than 8 (35.5% of patients with symptomatic BPH evaluated), 64% had no obstruction. In the same patient cohort, 51% of patients with an I-PSS of 0-7, 61% of those with an I-PSS of 8-19 and 63% of those with an I-PSS of 20 or greater had obstruction (44).

**Table 3. Clinical Prostate Score. Adapted from Rosier et al. 44.**

| | **No. of points** |
|---|---|
| **Prostate size ($cm^3$)** | |
| < 30 | 0 |
| 30-60 | 3 |
| > 60 | 6 |
| **Free maximal flow (mL/s)** | |
| > 12 | 0 |
| 8-12 | 5 |
| 4-8 | 10 |
| < 4 | 15 |
| Post-void residual urine volume (mL) | |
| < 30 | 0 |
| 30-100 | 2 |
| > 100 | 4 |
| **Voided volume (mL)** | |
| > 300 | 0 |
| 200-300 | 1 |
| < 200 | 2 |

### 3.1.3 Danish Prostate Symptom Score (DAN-PSS)

The DAN-PSS system is a self-administrated quality-of-life questionnaire comprising 12 questions related to

voiding problems and the perceived bother related to each individual symptom (Table 4) (45). The difference between the DAN-PSS and the AUA/I-PSS system is that in the former (DAN-PSS system), each symptom is both quantified and qualified by determining a symptom score and a 'bother' score. This questionnaire demonstrated a high degree of construct validity, correlating with the Madsen-Iversen score system and with the patient's answers to questions about how bothersome their symptoms were. The DAN-PSS system discriminates clearly between patients with BPH and control subjects, and was sensitive to changes following BPH treatment. However, it is was not able to predict bladder outlet obstruction (46). The DAN-PSS and I-PSS indexes are correlated, and the DAN-PSS seems to be more sensitive to changes after pharmacological treatment than the I-PSS, Madsen-Iversen and Boyarsky symptom indexes (47).

**Table 4. The Danish Prostate Symptom Score. Adapted from Hansen et al. (45).**

Each question allows the patient to choose one of four answers.
For each question the patient scores 0-3 for severity of symptoms (A) and 0-3 for the degree of bother (B).

1A Hesitancy: Do you have to wait for urination to start?
Answers: 0 No; 1 Rarely; 2 Daily; 3 Every time
1B If you have to wait to start urination, is this a problem for you?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

2A Weak stream: Do you consider your urinary stream as:
Answers: 0 Normal; 1 Weak; 2 Very weak; 3 Dribbling
2B If your stream is weak or dribbling, is this a problem for you?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

3A Incomplete emptying: Do you feel you empty your bladder completely?
Answers: 0 Always; 1 Occasionally; 2 Rarely; 3 Never
3B If you feel that you do not empty your bladder completely, is this a problem for you?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

4A Straining: Do you have to strain to start and/or maintain urination?
Answers: 0 No; 1 Rarely; 2 Daily; 3 Always
4B If you have to strain, is this a problem for you?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

5A Daytime frequency: What is the longest interval between each urination, from when you wake up until you go to bed?
Answers: 0 More than 3 h; 1 2-3 h; 2 1-2 h: 3 Less than 1 h
5B Do you consider your frequency of urination a problem?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

6A Nocturia: How many times do you have to urinate during the night?
Answers: 0 None; 1 One to two times; 2 Three to four times; 3 Five times or more
6B If you have to urinate during the night, is this a problem for you?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

7A Urge: Do you experience an imperative (strong) urge to urinate?
Answers: 0 Never; 1 Rarely; 2 Daily; 3 Always
7B If you have an imperative (strong) urge to urinate, is this a problem for you?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

8A Urge incontinence: Is the urge to urinate so strong that urine starts to flow before you reach the toilet?
Answers: 0 Never; 1 Rarely; 2 Daily; 3 Every time
8B If the urge to urinate is so strong that urine starts to flow before you reach the toilet, is this a problem for you?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

9A Dysuria: Do you feel pain or have a burning feeling when you urinate?
Answers: 0 Never; 1 Rarely; 2 Daily; 3 Always
9B If it hurts or burns when you urinate, is this a problem for you?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

10A Post-micturition dribbling: Do you experience dribbling after voiding, when you feel you have finished urination?
Answers: 0 Never; 1 In the toilet; 2 Small amounts in the trousers; 3 Large amounts in the trousers
10B If you experience dribbling after voiding, is this a problem for you?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

11A Stress incontinence: Do you experience leakage of urine when physically active (e.g. lifting, sneezing, coughing)?
Answers: 0 Never; 1 Rarely; 2 Often; 3 Always
11B If you experience urinary leakage when physically active, is this a problem for you?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

12A Overflowlseeping incontinence: Do you experience leakage of urine without urge or physical activity?
Answers: 0 Never; 1 Rarely; 2 Often; 3 Always
12B If you experience urinary leakage without urge or physical activity, do you consider this a problem?
Answers: 0 No problem; 1 Small problem; 2 Moderate problem; 3 Major problem

### 3.1.4 Quality-of-life assessment

The impact of urinary symptoms on quality-of-life is generally evaluated through question 8 of the I-PSS. However, this question measures the extent to which patients tolerate their symptoms rather than evaluating their quality of life. Many specific quality of life quality-of-life questionnaires have been used for clinical research. Among them, the Medical Outcomes Study 36-item short-form health survey (SF36) (48) is a self-administrated questionnaire used to measure general health status and quality of life. Using this score, a postal population survey among 217 men aged 55 years and over with LUTS showed that, depending on the activity, 9-49% of those with moderate or severe urinary symptoms reported interference with some of their daily activities. Increasing symptom severity was associated with worsening physical condition, social functioning, vitality, mental health and perception of general health. Increasing ‘bothersomeness’ was associated with worsening of all dimensions of general health status and quality of life. The association between the outcome of this population survey and the degree of ‘bothersomeness’ was stronger than that with the I-PSS symptom score. Longitudinal studies are needed to determine whether or not this quality-of-life approach to LUTS can provide a decision tool for treatment.

### 3.1.5 Baseline symptom score: age and hereditary factors

Age is one of the principal factors influencing the relationship between symptom score, flow rate and prostate volume. For each decade over 40 years of age, the decrease in peak and mean flow rates has been found to be similar (0.5 and 0.4 mL/s) (49). The increase in prostate volume and in total symptom score per decade of age was 3.3 mL and 0.6 mL, respectively.
Heredity appears to account for 82.6% of the variability in symptom scores in men older than 50 years. Monozygotic and dizygotic twin pairs were studied to determine age and LUTS as assessed by AUA symptom scores. Prostate volumes were measured by transrectal ultrasonography (TRUS). Results showed that there was a significant pairwise correlation between transition zone and symptom score, and between age and symptom score. Age also correlated significantly with all volume measurements.
Heredity appears to play an important role in the variability of frequency, urgency and straining. Weaker hereditary influences were observed for incomplete emptying and nocturia. There was no evidence that intermittency and weak stream were inherited (50).

### 3.1.6 Symptom score as decision tools for treatment

Symptoms are the most common reason for patients to seek medical care. The level of symptoms and their bothersomeness for the patient are important indicators of the need for medical intervention and are important means of evaluating the success of intervention.
In a prospective study involving 145 previously untreated patients with BPH symptoms, the treatment decision was based on the AUA symptom score (51). Patients with mild symptoms (0-7) were monitored only (WW), while those with moderate and severe symptoms were offered WW, finasteride, alpha-blockers, or laser prostatectomy or TURP. Overall, with a minimum follow-up of 2 years, 76% of the patients were still receiving their original therapy at 1 year and 68% at 2 years. A total of 81% of patients with mild symptoms remained on WW. Sixty per cent of patients with moderate symptoms remained on WW, 75% remained on alpha-blockers and 60% remained on finasteride. Of the patients with severe symptoms, 20% remained on WW, 17% remained on finasteride, 60% remained on alpha-blockers, while 60% of patients who underwent laser prostatectomy and 100% of those who underwent TURP received no further treatment (51).

These data suggest that symptom scores could provide a rational approach for the evaluation and management of patients with symptomatic BPH. However, different studies have shown only a poor correlation between symptoms and bladder outlet obstruction, and considerable spontaneous variability exists between I-PSS results in the same patient at baseline and a few weeks later, without any treatment (39).

### 3.1.7 Symptom score as outcome predictor

There is general agreement that poor response to surgical treatment (transurethral resection) is seen mostly in patients with low symptom scores (41-53). Patients with a greater pre-operative I-PSS score gained the most symptomatic benefit. The positive predictive value of a significant post-operative improvement of at least 7 I-PSS points, depended on the pre-operative I-PSS criteria applied. With a pre-operative I-PSS score of more than 17, the positive predictive value was 87%, with a corresponding negative predictive value of 71%.
When a post-operative improvement of 10 points, which corresponded to an improvement of approximately 3 points in the quality of life, was chosen as a clinically significant improvement, the calculated ROC (Receiver Operating Characteristics) curve indicated that the pre-operative I-PSS score could predict symptomatic outcome with good sensitivity and moderate specificity (52). Investigating 249 men undergoing TURP with symptom scores (Madsen and Iversen), Bruskewitz *et al*. recently confirmed that patients with the highest symptom scores were most likely to have show symptom improvement and those most bothered by the symptoms were most likely to have show an improvement in their quality of life (53).
The most significant baseline test, with which to measure substantially decreased urinary symptoms following TURP, is a greater level of baseline symptoms themselves, specifically obstructive symptoms. Baseline irritative symptoms also have an impact on predicting a decrease in symptoms, but their clinical contribution is limited. In contrast, patients with a high irritative symptom score fared best after transurethral microwave thermotherapy (TUMT) type Prostatron®, 2.0 (54). However, when attempting to construct nomograms to predict the outcome of high-energy thermotherapy (TUMT), multivariate logistic regression analysis showed that the four variables were independently predictive of response (age, prostate volume, obstruction grade [defined by LinPURR (Linear Passive Urethral Resistance Relation)] and TUMT energy), but not symptom score (55).

### 3.1.8 Conclusions

A symptom score is part of the baseline evaluation of a patient with BPH. It should only be used to describe and quantify BPH symptoms and to evaluate treatment outcomes objectively. Symptom scores alone should not be used to select the treatment of a particular patient.

## 3.2 Prostate-specific antigen (PSA) measurement

In the Agency for Health Care Policy and Research (AHCPR) guidelines, the measurement of PSA was optional (56). During the Fourth International Consultation on BPH that took place in Paris in 1997, all the available literature until that period was evaluated and the following conclusions were drawn (57):

- PSA measurement should be offered to men with LUTS and a life expectancy of over 10 years in whom the diagnosis of prostate cancer, once established, would change the treatment plan.
- The benefits and risks, including the likelihood of a false-positive or false-negative PSA test and the potential need for a TRUS-guided biopsy, should be discussed with the patient.
- It has been suggested that newer concepts, such as PSA density, PSA velocity and age-specific reference ranges, may enhance the statistical performance of PSA as a cancer-screening test. Until the results of definite studies are available, physicians must use clinical judgement to determine which patient should or should not undergo TRUS and TRUS-guided biopsy.
- New assays separating free and complexed PSA are being developed. These are believed to enhance the statistical performance of PSA as a cancer-screening test in the critical range of total PSA values between 2.0 and 10.0 ng/mL.

The reasons for these differences in the guidelines from various study groups are due to overlapping values of PSA among BPH patients and those with localized prostatic carcinoma. More importantly, it is still debatable whether or not early detection decreases the mortality from prostatic cancer. If PSA is going to be used in screening, problems arise in those cases in which the digital rectal examination (DRE) is normal and PSA values are in the ‘grey zone’ (4-10 ng/mL).
The concepts of PSA density and PSA velocity were first introduced in order to find criteria that urologists could use to decide which patients should be biopsied. Despite early enthusiasm and promising results reported in the first studies (58-60), further reports have questioned the effectiveness of PSA density and PSA velocity (61-63). In a recent study, Abdalla *et al*. (64) found that African-Americans had higher serum PSA levels and PSA densities than whites and Hispanics, so race and ethnicity must also be taken into account when evaluating parameters such as PSA density and PSA velocity.
Djavan and co-workers (65) studied an interesting new idea by comparing the PSA density of the whole prostate

with that of the transition zone and free PSA. They found that for patients with PSA values of 4-10 ng/mL, the PSA density of the transition zone enhanced the specificity of serum PSA as a predictor for the occurance occurrence of BPH. Also, the PSA density of the transition zone was found to be more effective in prostates larger than 30 mL, while the free-PSA-to-total-PSA ratio, was of greater use in prostates smaller than 30 mL. Age-specific reference ranges were introduced by Oesterling *et al*. (66) in order to improve the sensitivity of cancer detection in young men and the specificity of prostate cancer detection in older patients. The specific reference ranges proposed by Oesterling *et al*. were found to be inadequate for blacks as they would miss 40% of cancers in this ethnic subgroup (67). A study by Borer *et al*. (68) found that 60% of cancers missed using age-specific reference ranges had unfavourable histology. In another study, Bassler *et al*. (69) found that raising the upper limit of normal PSA from 4.01 ng/mL to 4.5 ng/mL resulted in failure to detect a substantial number of clinically significant cancers. Crawford and co-workers (70) examined the efficiency of PSA and DRE in screening using 4.0 ng/mL and age-specific reference ranges as a cut-off for abnormal values. They found that by using these reference ranges they could avoid unnecessary biopsies. However, fewer cancers were detected, so they concluded that a cut-off value of 4.0 ng/mL instead of age-specific reference ranges should be used in combination with DRE in screening programmes.

Measurement of the percentage of free PSA and its ratio to total PSA has been introduced in the last 8 years in clinical urological practice (71-73). It is believed that this ratio offers valuable information to help in selecting the right candidates for biopsy among patients with PSA values in the 'grey-zone'. In the last 2 years, numerous studies from all over the world have been published supporting the idea that the free/total PSA ratio improves the differentiation of benign disease and prostatic carcinoma (74-82). Letran *et al*. (83) found that the free/total PSA ratio could be used to predict cancer in patients undergoing repeat biopsies due to persistently elevated serum PSA levels. Simultaneously, other studies showed that the free/total PSA value reduced the negative biopsy rate (84).

Despite all these studies, there is still no consensus as to which critical cut-off value of free/total PSA ratio should be used. In another study, Paus *et al*. (85) noted an important in-vitro instability of free PSA in serum and large inter-individual differences. Jung *et al*. (86) also found that the free/total PSA ratio could not distinguish between patients with prostate cancer and those with chronic prostatitis. De la Taille *et al*. (87) compared three different immuno-assays for total and free PSA (Hybritech, Cis-Bio and Immunocorp), and found that all of them could distinguish prostate cancer from BPH, but at different cut-off values. Similar conclusions were reported by Nixon *et al*. (88), who compared the Hybritech, Dianon and Chiron assays. Tornblom *et al*. (89) used the percentage of free PSA in men with PSA values less than 3.0 ng/mL, and found that when it was greater than 18% in this group of patients, the risk of cancer was very low. In men receiving finasteride, Pannek *et al*. (90) found that total PSA serum levels decreased by 50%, but free PSA did not. Finally, Roehrborn *et al*. examined the use of PSA in patients undergoing evaluation for BPH. In one study, the utility of PSA as a predictor of prostate volume was evaluated; PSA and prostate volume were found to have an age-dependent, log-linear relationship (91). In a second study, serum PSA and prostate volume were shown to be powerful predictors of the risk of acute urinary retention and the need for BPH-related surgery in men with BPH (92).

### 3.2.1 Conclusions

The conclusions of the 1997 International Consensus Meeting on BPH are still valid and the recommendations should be adopted. PSA density, PSA velocity and PSA free/total ratio might offer valuable information in a subgroup of patients.

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## 3.3 Creatinine measurement

It is well-accepted today that bladder outlet obstruction due to BPH might cause hydronephrosis and renal failure (1). Ten years ago, it was shown that patients with BPH and renal insufficiency had a 25% risk of developing post-operative complications compared with the 17% risk in patients with normal renal function (2). Earlier studies also showed a much higher mortality among BPH patients who underwent surgical treatment when renal insufficiency was present at the same time (3,4).

Most studies have found that the incidence of azotaemia in men with BPH varies from 15% to 30% (5,6). However, these figures might be overestimates as these studies involved patients undergoing surgical treatment (i.e. those with severe symptoms and with urinary retention). A recent study evaluated 246 men presenting with BPH symptoms and found that approximately one in 10 (11%) had renal insufficiency (7). It was also shown that neither the symptom score nor the quality-of-life assessment was associated with serum creatinine levels in patients with BPH. When renal dysfunction was present, diabetes and hypertension were the most probable causes of the elevated creatinine level among this group of patients. This study also noted that it was rather rare to find patients with high creatinine levels due to bladder outlet obstruction only.

Comiter *et al*. (8) reported a study in which voiding dysfunction of a non-neurogenic aetiology did not appear to be a risk factor for elevated BUN (bloodurea urea/nitrogen) and creatinine levels. Bruskewitz *et al*. (9) also found that an isolated serum creatinine level could not predict the outcome after TURP, as measured by an improvement in quality of life. Despite all of the above, it is probably unwise to avoid measuring serum creatinine levels in patients undergoing BPH evaluation in an effort to minimize costs. Koch *et al*. (10) studied the additional value of renal ultrasonography in the assessment of patients with BPH and concluded that only those with an elevated creatinine level needed such an investigation.

### 3.3.1 Conclusions

As it is difficult to select those with renal insufficiency from among evaluable BPH patients, it is probably cost-effective to measure serum creatinine levels in all patients. In this way, proper therapy can be offered to the correct patients and the costs of long-term renal damage and post-surgical complications can be avoided. This point is increasingly emphasized, as the use of certain alpha-blockers might cause additional problems in men with renal insufficiency. In the report from the AHCPR (11) and in the recommendations of the Fourth International Consultation on BPH (12), the measurement of serum creatinine is highly recommended.

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### 3.4 Digital rectal examination (DRE)

DRE is an important examination in men with LUTS for two reasons. First, it can help to determine the co-existence of prostatic carcinoma. Second, it enhances the capacity to estimate prostate volume, and in this way might assist in choosing the right treatment, as prostate size has been shown to be a determining factor for certain treatment options. DRE is recommended in the AHCPR guidelines (1) and is highly recommended by the Fourth International Consultation (2).

#### 3.4.1 DRE and cancer detection

During the Fourth International Consultation meeting in Paris, all the available literature up to 1997 was evaluated and the conclusion was that the probability of a man with a suspicious DRE actually having cancer is was almost one in three (PPV - Predictive Positive Value, 22-34%). These figures are based on screening studies, and it is considered that DRE will have a higher PPV for cancer among patients with LUTS, as these patients are usually older.

During the last 2 years, numerous studies have been published concerning DRE and cancer detection. Among the various parameters examined with DRE, it has been postulated that prostate asymmetry might be an indicator of prostate cancer. Hansen *et al*. (3) examined 963 men with DRE and with serial monitoring of PSA, concluded that prostatic biopsy was not mandatory in an asymmetric prostate with no abnormality in PSA. Smith *et al*. (4) examined racial differences in the operating characteristics of prostate cancer screening tests. They found that the PPV of DRE was greater in black men than in white men (38% vs. 22%) and that PSA detected more cancers than DRE in both races, although this advantage was more pronounced in black men. Five studies during the past 2 years concur that, for PSA values greater than 4.0 ng/mL, DRE in combination with PSA serves effectively in screening for the early detection of prostate cancer by providing higher detection rates (5-9). However, it should be mentioned that for patients who are candidates for open prostatectomy and whose PSA is greater than 4.0 ng/mL, prostatic biopsy will detect cancer in 10% of cases, and these are men with no abnormality on DRE (10).

An important new question is: what is the value of DRE in detecting prostate cancer in patients with PSA levels less than 4.0 ng/mL? In a recent study, Carvalhal *et al*. addressed this question and concluded that the PPV of a suspicious DRE was 5%, 14% and 30% in men with 0-1.0, 1.1-2.5 and 2.6-4.0 ng/mL PSA, respectively (11). These findings contradict the results of three other studies in which DRE had a poor performance in low PSA

ranges and, as a result, it was not recommended for such screening programmes (12-14). McNaughton *et al*. questioned the value of DRE by introducing the concept of serendipity (15), which was defined as the discovery of a prostate cancer by random biopsy of an area of the prostate gland other than the palpable suspicious area that prompted the biopsy. It was found that serendipity was responsible for the detection of more than 25% of DRE-detected cancers, suggesting an overestimation of the true informative value of DRE.
Another important question concerning DRE as a screening tool is whether or not it affects prostate cancer mortality. Two studies that have been published in the last 2 years contradict each other: Jacobsen *et al*. (16) found a strong inverse association between DRE and prostate cancer mortality, while Richert-Boe *et al*. (17) suggested that DRE screening did not reduce mortality from prostate cancer.

### 3.4.2 DRE and prostate size evaluation

A number of options are currently available for the treatment of patients with BPH. Response to certain types of therapy (e.g. finasteride) depends on the actual prostate volume. In patients where invasive therapy such as surgery is recommended, estimation of the volume of the prostate gland will help the urologist to select the most suitable form of treatment with the lowest cost and the best outcome.
It should be noted, however, that prostate size does not correlate with symptom score or with the degree of urodynamic obstruction (18-20). It is well well-accepted that TRUS is more accurate in determining prostate volume than DRE. Roehrborn has analysed the data from four studies in which estimations of prostate volume by DRE were compared with those performed by TRUS (21). Despite the fact that different methods and criteria were used among the four studies, it was concluded that underestimation of DRE increased with increasing TRUS volume, particularly if the volume was greater than 30 mL. For this reason, Roehrborn developed a model of visual aids to help urologists to make a more accurate prediction of prostate volume.

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## 3.5 Imaging of the urinary tract

Imaging of the entire (including the upper) urinary tract, particularly prior to prostate surgery, has been an integral part of the diagnostic assessment of elderly men with LUTS due to BPH during past decades (1-12). In parallel with endoscopy, the role of routine imaging of the upper and lower urinary tract in all patients with LUTS has been increasingly questioned in recent years (5,6,9,13). Ideally, an imaging modality for patients with LUTS should provide both imaging of the urinary tract and demonstrate the morphological effects of prostate pathology upon the rest of the lower and/or upper urinary tract.

### 3.5.1 Upper urinary tract

A recent survey of 24 urological centres in the UK showed that 21 of 24 centres (79%) used either intravenous urography (IVU) or sonography, and that 16 of 24 centres (67%) used plain films as routine procedures prior to prostatectomy (14). Similar findings, particularly a high rate of IVU, have been reported in the USA (15). The most common argument in favour of routine imaging of the upper urinary tract was “not to miss anything”.
Data from several large-scale studies have led to doubts concerning the role of routine upper urinary tract imaging in patients with LUTS. Wilkinson and Wild (12) reported on 175 patients with LUTS with no urinary retention and identified no abnormalities on renal ultrasound and IVU that would have altered the therapeutic approach. Similar data have been published by Koch *et al*, who performed renal ultrasound scans in a consecutive series of 556 elderly men with LUTS; 14 (2.5%) had hydronephrosis (13). Serum creatinine levels appeared to be correlated with dilatation of the renal pelvis. The authors concluded that renal ultrasound is only indicated in patients with an elevated serum creatinine level and/or post-void residual urine volume (13).
A recent review was carried out on data from 25 published reports on the findings of IVU. A total of 6,131 men from nine ultrasound series were involved, including included 778 patients with LUTS due to BPH. The mean patient age in these series was 68.4 years (16). Overall, 74.3% of all IVUs and 70% of all the ultrasound studies performed were normal. Hydronephrosis was found in 7.6% IVU and 6.8% ultrasonography patients; 30% had measurable degrees of renal insufficiency. Poor or no renal function was found in 12.3% and 0.8%, Renal cysts were seen in 4.5% and 15.3%, and solid renal masses were identified in 0.81% and 0.51% of IVU and ultrasonography patients, respectively.

These data need to be correlated with the incidence of renal cell cancer in the general population. Based on a several autopsy and epidemiological studies, it has been estimated that the risk of elderly men developing renal cell cancer ranges from 0.18% to 0.56%. These figures are comparable with the results of large-scale studies in elderly men with LUTS and indicate that the incidence of renal carcinoma is not increased in these patients.
Other malignancies found during routine examination of the urinary tract are bladder and ureteral cancer, usually

seen in about 1% of cases. However, most of the cancers suspected during imaging were not identified during endoscopy. A number of tumours were identified during endoscopy that had been overlooked during imaging.

IVU adverse events: A review of 10 reported studies involving over 2.1 million patients revealed an incidence of adverse effects due to contrast medium in approximately 6% of patients, an incidence of serious adverse effects in 1 in 1,000-2,000, and a risk of dying from an allergic reaction of 1 in 100,000-200,000 (17,18). The average radiation dose is 1.58 rem. Low-osmolar contrast material (LOCM) resulted in a six-fold improvement in safety compared with high-osmolar contrast material (18). Furthermore, in patients with pre-existing renal failure, the use of LOCM reduces the risk of nephrotoxicity (18).

IVU or renal ultrasound: Several arguments support the use of renal ultrasound. Among the most important are:
- Better characterization of renal masses
- The possibility of investigating the liver and retroperitoneum
- Simultaneous evaluation of the bladder, post-void residual urine volume and prostate
- Costs
- Avoidance of irradiation
- No side-effects

### 3.5.2 Lower urinary tract

Urinary bladder voiding cysto-urethrogram: This investigation suffers from the fact that the information on the lower urinary tract is only indirect and gives, at best, only limited urodynamic information. It is therefore not recommended in the routine diagnostic work-up of elderly men with LUTS. More recently, the measurement of the bladder wall thickness by transabdominal ultrasound has gained considerable interest as a non-invasive tool to assess bladder outflow obstruction (19). Manieri *et al*. (20) concluded that bladder wall thickness appeared to be a useful predictor of bladder outlet obstruction, with a value exceeding that of uroflowmetry. Reliable data on inter- and intra-observer variability, as well as reproducibility, are still lacking and, therefore, measurement of the bladder wall thickness is currently not part of the recommended diagnostic test for the diagnostic work-up of patients with LUTS.

### 3.5.3 Urethra

Retrograde urethrography gives only indirect information on the effect of benign prostatic enlargement (BPE) on adjacent structures.

### 3.5.4 Prostate

Imaging of the prostate is performed to assess:
- Prostate size
- Prostate shape
- Occult carcinoma
- Tissue characterization.

The prostate can be imaged using:
- Transabdominal ultrasound
- TRUS
- Computed tomography (CT) and magnetic resonance imaging (MRI) (including transrectal MRI).

In daily routine practice, however, only imaging of the prostate by TRUS or, if this is not available, by transabdominal ultrasound, is currently used (21).

Prostate size: A large body of evidence documents the accuracy of TRUS in calculating the volume of the prostate (22,23). TRUS has significantly higher accuracy than that of cystoscopy, IVU, rectal examination and or urethral pressure profile (24). The prostate volume estimated by DRE and endoscopy is known to underestimate prostates over 40 mL in size (24). Prostate volume can be estimated by serial planimetry, orthogonal plane, rotational body (single plane, ellipsoid) and three-dimensional methods (23).

Clinical relevance of prostate size: A number of studies indicate that prostate size is a (weak) outcome predictor in the emerging field of less invasive procedures. Outcome is usually more favourable in patients with smaller prostates, particularly for visual laser ablation (VLAP), interstitial laser coagulation (ILC), transurethral electrovaporization (TUVP) and (TUNA®). However, there is no generally accepted volume for which these less invasive procedures are contraindicated. In contrast, it has been demonstrated that high-energy (TUMT) is more suitable for patients with larger prostates. With transurethral/open prostatectomy, the critical volume is

approximately 80 mL, while for transurethral incision of the prostate (TUIP) or TURP the critical volume is 25-30 mL. For finasteride therapy, the critical volume is 40 mL.

Prostate shape: Watanabe (25) introduced the concept of the presumed circle area ratio (PCAR). This is based on the usual normal triangular-shaped appearance of the prostate in the absence of BPE. With BPE, the shape of the prostate is changed by the continuous growth of the transition zone. Watanabe reported that pathological residual urine is seen if the PCAR is greater than 0.75 or less than 75, and that BPE is very unlikely to be the cause of the post-void residual urine volume. More likely causes include bladder cancer or prostate cancer. However, validation of these data by others is still lacking.

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## 3.6 Voiding charts (diaries)

Voiding charts (diaries) are recommended in both the AHCPR guidelines (1) and the Fourth International Consultation on BPH (2). They are simple to complete and can provide useful objective clinical information. There is no standard frequency volume chart, but the simplest is probably the 7-day chart recommended by Abrams and Klevmark (1,3). is probably the simplest. A close correlation exists between LUTS and frequency volume chart data, particularly nocturia (4,5). The ICS BPH study (4) reported an exact correlation in 41% of the number of voids, 61% for the time of void and 68% for episodes of nocturia. Although voiding charts will not diagnose obstruction or detrusor instability, they can be of great benefit in quantifying symptoms and assessing response to treatment (6). Data collected by patients is both reliable and reproducible (7).

### 3.6.1 Conclusions

Recording a 24-hour frequency volume chart prior to initial consultation is optional. However, all patients with LUTS should be asked to bring a completed frequency volume chart to their initial consultation. The use of these recordings allows the identification of patients with idiopathic nocturia or excessive fluid intake. The frequency-voiding chart objectively quantifies diurnal frequency, nocturia, voiding volumes and patterns.

## 3.7 Flow rates

Flow rate analysis is optional in the AHCPR guidelines (1) and is recommended by the Fourth International Consultation on BPH (2). A review of the literature indicates that uroflowmetry should be performed as part of the diagnostic assessment of patients who have LUTS suggestive of benign prostatic obstruction, and is obligatory prior to undertaking surgical treatment. It is a simple, non-invasive test that can reveal abnormal voiding. Flow-rate analysis will not distinguish between patients with bladder outflow obstruction and those with low detrusor pressure, or between those with high pressure but normal flow. Approximately one-third of patients with flow rates over 10 mL/s are not obstructed, and pressure-flow analysis in this group should be considered prior to surgical intervention. Uroflowmetry is not predictive of outcome with medical treatment.

The flow rate machine provides a printout reading for voided volume, maximum flow (Qmax), average flow (Qave) and time to Qmax. The software used is unable to identify artefacts caused by abdominal straining, splashing or voiding directly down the funnel. For this reason the clinician must interpret each flow rate to exclude artefacts (8,9). Flow curve patterns may be classified into five separate groups (10).

Performance anxiety can result in the flow test being non-representative (11), and it is therefore important to ask whether or not the patient felt the flow test obtained truly reflected the normal voiding pattern. In order to obtain a more representative flow test, serial flows (two or more) are recommended, so that the patient can ‘learn’ the technique and have the opportunity to void with a full bladder. Home uroflowmetry is an extension of this approach to allow flow rate data to be obtained in the relaxed environment of the home. A close relationship between home and outpatient flows has been reported (12), although Qmax in the outpatient setting is slightly higher due to the increased volume voided. Whether at home or in the clinic, there can be significant intrapatient variation (13).

Nomograms from Bristol, Siroky, Liverpool, Balsev-Jorgensen and the Olmstead County study all confirm a relationship between voided volume and flow rates. The nomograms are also age-dependent. Small voided volumes result in a reduction in Qmax to the extent that voided volumes of less than 150 mL do not provide reliable results (14). A voided volume of less than 150 mL is also associated with a higher incidence of

obstruction on pressure-flow analysis (4). McConnell *et al*. (15) reviewed 12 studies and demonstrated a clear relationship between flow and voided volume, with a significantly reduced flow rate if the flow was less than 150 mL. Various manipulations of the standard flow rate data have been made in order to improve diagnostic accuracy in low voided volume tests. These include Qm90 (mean flow for middle 90% of voided volume), dI/dt40 (velocity of detrusor contraction at 40 mL volume) and Tdesc (time from Qmax until 95% of volume voided). However, these alternative measurements do not improve the prediction of bladder outflow obstruction from low-volume voids.

Obstruction can only be diagnosed with a pressure-flow test. However, provided a technically satisfactory flow rate has been obtained (> 150 mL), it is possible to predict the likelihood of obstruction:

- Qmax < 10mL/s: 90% bladder outflow obstruction based on cystometrogram
- Qmax 10-14 mL/s: 67%
- Qmax > 15 mL/s: 30%.

The probability of obstruction with a flow rate of more than 10 mL/s in elderly men (> 80 years) falls to 40%. In view of age-related urodynamic changes in elderly patients with BPH, flow rates must be interpreted with caution (16).

There are conflicting data on the prediction of outcome following TURP on the basis of flow rates. Of the few prospective studies performed, Jensen *et al*. (17) reported that patients with a Qmax of more than 15 mL/s have a less successful outcome following prostatectomy compared with those who have pre-operative flow rates below 15 mL/s (70% vs. 91%). Abrams (18) reported a reduced success rate if the pre-operative flow rate was normal. However, data from Neal *et al*. (19) failed to confirm such a relationship, with patients with high-pressure, high-flow bladders also gaining benefit from surgery. Two large studies showed no association between pre-treatment flow rates and symptomatic improvement with alpha-blocker therapy (20,21).

### 3.7.1 Conclusions

Qmax should be recorded from a minimum of two flow tests and the patient should consider the tests to be representative of his usual voiding pattern. All flow tests require interpretation rather than relying solely on data generated by the machine software in order to exclude artefacts. Patients should be made aware of the limitations of flow tests in the diagnosis of obstruction before consenting to invasive surgical treatments.

## 3.8 Post-void residual urine volume

Post-void residual urine volume is considered to be an optional test by the AHCPR (1), but is recommended by the Fourth International Consultation on BPH (2). This test is controversial because there is considerable intra-individual variation in residual urine volume (22).

Post-void residual urine volume should be calculated by the measurement of bladder height, width and length obtained by transabdominal ultrasonography in longitudinal and transverse planes. This is a simple, accurate and non-invasive method (23). No single formula has been adopted, but all those used commonly correlate closely (24). There is a wide variation in residual urine volume from one void to the next. Birch et al. (24) showed that 66% of patients have significant variations and Bruskewitz *et al*. (25) confirmed this observation. It appears that the larger the residual urine volume, the greater the overall variation.

The post-void residual urine volume does not correlate with symptoms, prostate size, flow rate or prostatic obstruction (26-29). Andersen (27) suggests that some patients with larger residual urine volumes progress more slowly. But these larger volumes eventually tend to lead to retention. However, it is known that men with post-void residual urine volumes greater than 350 mL are more likely to fail WW (28). It is also known that patients with chronic retention may have a worse result from prostatectomy.

The arbitrary figure of a post-void residual urine volume of more than 300 mL is taken to represent chronic retention. Large residual urine volumes may be associated with a less favourable outcome following prostatectomy; however, the literature is conflicting. In a group of 253 patients undergoing TURP, Neal *et al*. (29) reported that poor outcome was associated with a low voiding pressure and detrusor instability, but not with residual urine volume. Abrams et al. (30,31) reported a poor outcome in patients with low-pressure chronic retention. Styles *et al*. (32) looked at a group of 68 chronic retention patients and found that 32% of the men still had a large residual urine volume post-TURP, although this group could not be predicted by cystometry. Surprisingly, there is no evidence that post-void residual urine predisposes patients to urine infection (33).

Renal ultrasound is routinely performed in patients with chronic retention to exclude upper tract dilatation; however, Koch *et al*. (34) demonstrated that renal ultrasound is only of benefit when the serum creatinine level is elevated above the normal range. Provided serum creatinine has been measured, cases of upper tract dilatation secondary to chronic retention should not be missed.

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## 3.9 Urodynamic studies

Pressure-flow studies are regarded as an additional diagnostic test and are considered optional by both the AHCPR (1) and the Fourth International Consultation on BPH (2). Flow rates only determine the probability of obstruction, whereas pressure-flow studies can categorize the degree of obstruction and identify patients in whom a low flow rate may be due to a low-pressure detrusor contraction. Flow rates may be particularly limited in predicting obstruction in specific situations, such as in elderly patients, individuals with low voided volumes, or men with a Qmax of more than 10 mL/s, as well as in the presence of neurological disease. Although pressure-flow studies are the only means of diagnosing obstruction accurately, debate continues as to their role in predicting treatment outcomes. For this reason, and because pressure-flow studies are regarded as invasive, they remain optional. In specific patient subgroups, the case for pressure-flow studies is stronger.
The methodology for performing pressure-flow studies is now standardized (1) and requires the simultaneous recording of both intravesical and intra-abdominal pressure. Detrusor pressure at the point of maximum flow must be recorded in order to diagnose obstruction. Different nomograms exist with which to classify patients into categories of obstruction. Those developed by Schafer (4), Abrams and Griffiths (5) and Rollema and van Mastrigt (URA - Urethral Resistance Index) (6) are most commonly used, and they all correlate closely. The ICS (International Continence Society) nomogram (7) has now been adopted as the standard nomogram to aid comparison of different data sets, and should be used in clinical practice.

### 3.9.1 Outcome

Pressure-flow studies do not predict the response to medical therapy and have no role in this setting. However, it is known that patients with high-pressure and low-flow urodynamics have the best outcome from prostatectomy. Patients with low-pressure and low-flow urodynamics may also have a successful outcome following prostatectomy, but the probability is lower.
Most work in relation to pressure-flow studies and treatment of BPH relates to TURP. Studies from Neal *et al*. (8,9), Abrams *et al*. (10), Jensen (11), Robertson *et al*. (12) and Langen *et al*. (13) all report improved outcomes

in patients who are obstructed prior to surgery, based on pressure-flow studies. It must be remembered however, that some patients with high-pressure and high-flow, and others with low-pressure and low-flow, from urodynamic studies may also benefit from surgery, although the probability of a successful outcome is reduced.

### 3.9.2 Conclusions

Pressure-flow studies remain optional tests in straightforward cases presenting for the first time with LUTS. These studies are the most useful investigations available for the purpose of counselling patients regarding the outcome of surgical therapies for BPH. The ICS nomogram should be used for the diagnosis of obstruction in order to standardize data for comparative purposes.

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## 3.10 Endoscopy

The standard endoscopic procedure for diagnostic evaluation of the lower urinary tract (urethra, prostate, bladder neck and bladder) is a urethrocystoscopy. This investigation can confirm causes of outflow obstruction while eliminating intravesical abnormalities.

### 3.10.1 LUTS caused by bladder outlet obstruction

Voiding complaints in elderly men are most frequently caused by BPH resulting in benign prostatic obstruction.

This obstruction has a critical role in altering voiding, resulting in significant (pathological) changes in the urinary tract of some patients and symptoms alone in others. However, the role of BPH in the voiding dysfunction experienced by elderly men is often unclear (1). Hyperplasia may be associated with striking lateral lobe enlargement, but symptoms may be negligible if the degree of obstruction is not severe. Conversely, BPH may be associated with a relatively small prostate and marked obstructive symptoms if the obstructing tissue originates exclusively within the central zone of the peri-urethral gland area (2).
It is generally accepted that therapies aimed at removing obstruction will relieve LUTS in most men. Patients with BPH or other forms of bladder outlet obstruction may develop certain signs seen by urethrocystoscopy, indicating the presence of such obstruction. These signs may include:

- Enlargement of the prostate gland with visual obstruction of the urethra and the bladder neck
- Obstruction of the bladder neck by a high posterior lip of the bladder neck
- Muscular hypertrophy of the detrusor muscle, indicated by the presence of muscular trabeculation and the formation of cellules as well as diverticula
- Formation of bladder stones
- Retention of (post-void residual) urine

Thus, urethrocystoscopy may provide information as to the cause, size and severity of obstruction, patency of the bladder neck, prostatic occlusion of the urethra and estimated prostate size (3). Several studies have addressed these issues.

### 3.10.2 Morbidity of urethrocystoscopy

Berge *et al.* (4) studied 85 patients and found that the risk of acquiring clinically significant urinary tract infection was 2.4% after urethral instrumentation alone.

### 3.10.3 Relationship between trabeculation and peak flow rate

Shoukry *et al.* (5) evaluated 122 patients of mean age 64 years with LUTS using three post-operative uroflowmetry tests and symptom evaluation. Urethrocystoscopy was also performed in these patients. The pre-operative peak flow rate was normal in 25% of 60 patients who had no bladder trabeculation, 21% of 73 patients with mild trabeculation and 12% of 40 patients with marked trabeculation on cystoscopy. All 21 patients who presented with diverticula had an ‘obstructive’ peak flow rate prior to surgery.
Anikwe (6) showed that there was no significant correlation ($p > 0.5$) between the degree of trabeculation, as graded from I to IV, and the peak pre-operative flow rate in 39 men aged 53-83 years with LUTS. There did appear to be a trend towards lower peak flow rates in men with higher degrees of trabeculation.

### 3.10.4 Relationship between trabeculation and symptoms

Simonsen *et al*. (7) found a correlation between the presence of trabeculation and the number of obstructive symptoms. When patients were grouped by age, it was noted that trabeculation significantly increased with increasing age ($p < 0.5$). In another study, none of the trabeculation ratings were predictive of symptom severity, while moderate-to-severe trabeculation was predictive of larger prostate size and reduced flow rate (8).

### 3.10.5 Relationship between trabeculation and prostate size

Anderson and Nordling (9) examined the correlation between cystoscopic findings and the presence of trabeculation. While the cystoscopically estimated weight correlated with the presence of trabeculation ($p = 0.003$), the bladder neck to verumontanum distance and the cystoscopic appearance of occlusion did not correlate significantly ($p > 0.5$). Homma *et al.* (10) showed that patients had a high likelihood of outlet obstruction when their prostate size was greater than 30 mL or if their posterior urethra was severely obstructed on endoscopy.

### 3.10.6 Relationship between trabeculation and obstruction

Ezz El Din *et al*. (11) evaluated urethroscopic findings and the results of urodynamic studies in 492 elderly men with LUTS. They noted a clear correlation between cystoscopic appearance (grade of trabeculation and grade of urethral obstruction) and urodynamic indices, detrusor instability and low compliance. It should be noted, however, that bladder outlet obstruction is present in approximately 15% of patients with normal cystoscopic findings, while approximately 8% of patients have no obstruction at all even if severe trabeculation is present, suggesting the inadvisability of drawing the same conclusion in all patients. They believe that the value of urethrocystoscopy is limited and advise against its use in the diagnosis of bladder outlet obstruction. Instead, it should be used primarily to exclude bladder pathology and to decide between interventional approaches.

### 3.10.7 Bladder diverticula and obstruction

The detection of large bladder diverticula might be of therapeutic importance. For example, the presence of a

large bladder diverticulum might dictate the type of intervention. It is, however, evident that other diagnostic modalities, such as the cystography, intravenous pyelography (IVP) or transabdominal sonography, are equally sensitive, or more sensitive, at detecting large bladder diverticula, without carrying the risks of invasive urethrocystoscopy. No data are available to document the sensitivity or specificity of cystography, IVP, cystoscopy or transabdominal sonography for evaluating large bladder diverticula.

Quirinia and Hoffmann (12) reported on 104 patients with BPH of whom 51% had diverticula by cystography. Although the presence of diverticula was related to age, upper tract dilation, increasing amounts of residual urine and bladder instability, there was no relationship with bladder capacity, peak flow rate or prostate size. At present, no final decision about the value of cystoscopy in the assessment of bladder diverticula can be made. Equally poorly documented is the impact that the presence or absence of bladder diverticula might have on outcome after prostate surgery.

### 3.10.8 Bladder stones and obstruction

There is no doubt that the presence of bladder stones can be assessed accurately by urethrocystoscopy. Bladder stones are a clear indicator of bladder outlet obstruction. While it is not always clear whether the obstruction is of an organic, anatomical or neurogenic nature, the presence of stones in the bladder indicates an abnormality in the bladder-emptying mechanism and is usually preceded by the presence of residual urine or recurrent urinary tract infections. However, there is also no doubt that bladder stones are detected equally well by IVP or by the non-invasive method of transabdominal sonography. In fact, stones composed of poorly radio-opaque or radiolucent material are seen very well by transabdominal sonography, while being missed on a renal ultrasound.

The crux of the matter has to be whether or not the detection of bladder stones dictates the surgical procedure of choice. It is obvious that the presence of a large bladder stone should guide the surgeon towards an open procedure rather than a lengthy electrohydraulic lithotripsy. However, the majority of all bladder stones are rather small, and can be removed during TURP through the sheath of the resectoscope, or by destroying them with endoscopic instruments prior to washing them out. It is therefore questionable whether or not urethrocystoscopy should be performed to assess the presence or absence of bladder stones prior to surgery for BPH, particularly as most patients with bladder stones will have microscopic haematuria that will have been detected during the standard basic evaluation.

### 3.10.9 Intravesical pathology

The detection of other pathology (urethral or intravesical) is advantageous and can be accomplished by endoscopy better than with most other modalities. In a study by Ezz El Din *et al*. (13), urinalysis and a cystoscopy were performed in 750 consecutive patients with BPH. Only three patients had a bladder tumour while 49 had urinary calculi. There was no correlation between any clinical parameter and the finding of microscopic haematuria. It was concluded that haematuria is a frequent finding in the assessment of BPH patients and that additional tests should only be performed if indicated (e.g. in the case of abnormal urine cytology).

### 3.10.10 Conclusions

Diagnostic endoscopy of the lower urinary tract should be considered an optional test for the following reasons:

- The outcomes of the intervention are unknown
- The benefits do not outweigh the harm of the invasive study
- Patients' preferences are expected to be divided

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### 3.11 RECOMMENDATIONS FOR DIAGNOSIS

1. Among all the different urinary symptom score systems currently available, the use of I-PSS is recommended because of its worldwide distribution and use.
2. In patients undergoing investigation for LUTS, the minimal requirement is to assess the upper urinary tract function with a creatinine measurement and/or an ultrasonographic examination.
3. DRE is a minimal requirement in patients undergoing investigation for LUTS.
4. There is a consensus that if imaging of the upper urinary tract is performed, ultrasonography is the method of choice.
5. Imaging of the upper urinary tract is recommended in patients with LUTS and one of the following:
   - History of, or a current, urinary tract infection
   - History of urolithiasis
   - History of urinary tract surgery
   - History of urothelial tumour (including IVU)
   - Haematuria (including IVU)
   - Urinary retention
6. CT and MRI currently have no place in the routine imaging of the upper urinary tract in elderly men with LUTS.
7. Routine imaging of the urinary bladder cannot be recommended as a diagnostic test in the work-up of patients with LUTS. Ultrasound of the bladder, however, is a valuable diagnostic tool for the detection of bladder diverticula or bladder stones.
8. Routine imaging of the urethra is not recommended in the diagnostic work-up of patients with LUTS.
9. The method of choice for the determination of prostate volume is ultrasonography, preferably via the transrectal route. However, imaging of the prostate by transabdominal ultrasound and TRUS is optional.
10. Prostate size should be assessed when considering open prostatectomy and TUIP, and prior to finasteride therapy.
11. If the voided volume is less than 150 mL or Qmax is greater than 10 mL/sec, pressure-flow studies should be considered before surgical intervention, particularly in elderly men.
12. Measurement of residual urine volume is a recommended test in the assessment of patients with LUTS suggestive of benign prostatic obstruction.
13. Endoscopy is recommended as a guideline at the time of surgical treatment to rule out other pathology and to assess the shape and size of the prostate, which may have an impact on the treatment modality chosen.
14. Pressure-flow studies should be considered for patients prior to surgical treatment in the following subgroups:
   - Younger men (e.g. < 50 years of age)
   - Elderly patients (i.e. > 80 years of age)
   - Post-void residual urine volume over 300 mL
   - Qmax more than 15 mL/s
   - Suspicion of neurogenic bladder dysfunction
   - After radical pelvic surgery
   - Previous unsuccessful invasive treatment

# 4. TREATMENT

## 4.1 Watchful Waiting (WW)

BPH affects the quality rather than the quantity of life. The treatment decision depends on patient preference, efficacy of the treatment in reducing obstruction, durability and cost, physician experience and availability of modalities (1). The construction of the therapeutic spectrum should be based on individualization and relevant factors. The choice of an inappropriate modality or selection of the wrong patient can lead to a cascade of therapies, with a consequent impact on quality of life and costs.

### 4.1.1 Assessment

There is no clear relationship between prostate size and symptoms, between prostate size and peak flow rate, or between prostate size and interference with activities of daily living or quality of life (2-4). However, 70% of urologists choose therapy intuitively or based on anecdotal experiences, 15% are undecided and only 15% base their decisions on the results of literature searches or Phase III studies (5).
A minimal subjective and objective assessment should be performed in all patients seeking consultation for BPH before deciding on the appropriate treatment modality. Symptoms must be assessed using the I-PSS and the objective assessment must include at least measurement of post-void residual urine volume and uroflowmetry. If pressure-flow studies are performed in mild symptomatic patients, clear obstruction will be seen in 20-32% of cases (6,7) and moderate obstruction in 36% of cases (6).
Between 44 and 68% of patients are non-obstructed (6,7). The obstruction status cannot be predicted from symptom score or prostate size, but the existence of post-void residual urine seems to be a clear predictor of obstruction, or at least indicates the need for a urodynamic study.

### 4.1.2 Procedure

The WW policy consists of no medical or surgical treatment.

### 4.1.3 Morbidity

The risk of serious sequelae following a WW policy is small (8). The only related morbidities are the development of acute urinary retention or impairment of renal function.
Studies show that the proportion of moderately symptomatic patients developing urinary retention is low (3.6-7%) (9,10). High residual urine volumes developed in 7% of patients, while the risk of developing renal azotaemia was insignificant (9).

### 4.1.4. Outcome: subjective, objective and urodynamics

Use of the WW policy is equal to allowing BPH to follow its natural history. Information regarding evolution of the condition can be obtained from retrospective, comparative and prospective studies and from the placebo arms of randomized, controlled trials (11,12). In general, the likelihood of poor outcome is small (9).

Subjective outcome: The majority of patients do not experience a worsening of symptoms over time. In a retrospective setting, 90% of patients on WW did not need any treatment, 32% reported some degree of improvement and 17% experienced symptomatic worsening (13). An analysis of patients on a waiting-list for surgery showed that after a mean period of 3 years, 70% did not experience any change in symptoms and 12% improved (14). Prospective studies confirm a low rate of worsening of symptoms of 0-21% with follow-up ranging from 6 months to 3 years (6,7,15). The situation remains stable in the majority of patients, but non-negligible symptomatic improvements (in 30-48% of patients) have been noted in some cases, even with long-term follow-up (15,16).

Witjes *et al*. (6) reported a significantly lower I-PSS in 64% of patients, lower nocturia (I-PSS) in 34% and better quality of life in 51% at 6 months of follow-up. However, the mean improvement was not clinically relevant. The same authors did not find any subjective improvement in obstructed patients (6).

Objective outcome - post-void residual urine volume: Post-void residual urine volume seems to increase in a small percentage of patients, found to be; 7% in the Veterans study (9). Nevertheless, considerations regarding the broad difference between the existence or otherwise of significant post-void residual urine made this figure of dubious value (17).

Urodynamics: Subjective differences do not always correlate with objective differences. There is no change in peak flow rate at 6 months of follow-up (6). When pressure-flow studies were performed, no change was found between the baseline and 6-month follow-up rate of non-obstructed, moderately, or obviously obstructed patients (6).

## 4.2 Need for treatment

In patients with moderate symptoms the global crossover to the need for treatment is 10-27% after 3-4 years of WW (3,9,10). The Kaplan-Meier estimated crossover rate at 5 years was 36% in the Veterans study, but as the failure rate with WW assessed objectively is less than this, it is possible that elective and true post-treatment failures may have been included in this figure (9).

The most significant baseline factors associated with crossover are bothersomeness, voided volume, residual urine and degenerative arthritis. Although symptom score was found to be a significant predictor, it was not significant in the Cox regression analysis, which found that bothersomeness was the most important predictive factor (9).

The natural history of BPH was assessed in the Baltimore Longitudinal Study of Aging. Predictive risk factors for subsequent surgery included changes in prostate size, force of the urinary stream and sensation of incomplete bladder emptying (18). If obstruction was present, 20% of the men experienced an increase in symptoms and required other treatment modalities (7).

## 4.3 Sexual function

There is a lack of information in the literature on this subject. As no medical or surgical treatments are used, no changes in sexual function would be expected with the WW policy other than those related to age and co-morbidity.

## 4.4 Durability and costs

The number of patients who remain on WW is approximately 85% at 1 year. The figures decrease slightly and progressively to 64% at 5 years (7,9,15,19). Costs are closely related to durability of treatment. The costs of different treatments are difficult to calculate, not only because of individual variations in health care systems but also because, in most cases, there is a mix and even an overlap of therapies over time. A model calculating cumulative health care costs for BPH treatment shows that the effectiveness of each type of therapy depends on the patient's age - surgery being more cost-effective at younger ages and medical treatment more cost-effective at older ages. Overall, the total cost of mixed medical treatment/surgery is consistently higher than that of either surgery or medical treatment alone, and more than double that of WW (20).

## 4.5 Patient selection

It is still difficult to identify which patient will respond to a particular treatment. The assignment of a patient to WW requires detailed evaluation if positive gains in health are to be achieved (2). Large intercountry variations have been described in the rate of patients assigned to WW policy (21,22). A recent survey of treatments for benign prostatic obstruction in the UK showed that urologists chose WW in 29% of cases (23).

The AHCPR guidelines on BPH recommend WW in patients with minimal symptoms (I-PSS, 0-7) that do not interfere with quality of life and who have no abnormalities in the initial evaluation (24). Only a small proportion of patients fall into this category; the majority belong to the 'grey areas' for which treatment choice varies according to the urologist and patient preferences (21). High symptom scores and low flow rates are associated with more aggressive treatment choices (19,21). In the Veterans study, the baseline factors most strongly associated with successful treatment outcome were baseline measures of high peak urinary flow rates, lower urinary bother and lower residual urine volume (9). Despite some weak points, this study provides the best available estimates for the outcome of WW strategies (8).

The ideal patient for WW is one with an I-PSS symptom score of less than 7 (mild symptoms that do not interfere with his daily life). If significant post-void residual urine volume is identified, a urodynamic study must be performed to rule out detrusor abnormalities. Although the presence of obstruction is not a formal contraindication for adopting a WW policy, obstructed patients are at high risk of needing other treatments (7,25).

## 4.6 Conclusions

- Assessment must involve at least I-PSS, measurement of post-void residual urine volume and peak flow rate.
- Until reliable factors predicting long-term complications are available, a multifactorial approach, combining the presence of symptoms, their bothersomeness and their influence on daily life, as well as cost-efficacy, must be taken into account before advising a WW policy.

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## 4.8 Medical treatment I: 5-alpha-reductase inhibitors and phytotherapy

### 4.8.1 Finasteride

Finasteride is the first 5-alpha-reductase inhibitor to be used in urological clinical practice. The biological rationale for using this compound in the treatment of BPH came from an early observation that patients with 5-alpha-reductase deficiency had non-palpable prostates (1). Today, after the completion of many trials, there is no doubt that finasteride can reduce the size of the prostate gland by 20-30%. It improves symptom scores by approximately 15% and can also cause a moderate improvement in urinary flow rate of 1.3-1.6 ml/s (2-4).

The efficacy of finasteride, however, was questioned by a study published in 1996 which showed that terazosin monotherapy and terazosin plus finasteride were more effective than finasteride monotherapy or placebo (5). Indeed, finasteride in this study was no more effective than placebo. A meta-analysis of six randomized clinical trials with finasteride was performed because the results of this study conflicted with those of all previous trials (6). The main conclusions of the meta-analysis were that baseline prostate volume was a key predictor of various treatment outcomes and that finasteride was more effective in prostates larger than 40 mL. During the Fourth International Consultation on Benign Prostatic Hyperplasia that took place in Paris in 1997, all the available data on this medical treatment option were analysed and the recommendation was: “Finasteride is less effective in men without enlarged prostates. Given its minimal side-effects finasteride should be considered an acceptable treatment option in men with clinically enlarged prostates” (7).

Recently, the Finasteride Urodynamics Study Group published the results of two studies verifying the above recommendation. In the first study it was shown that improvement in pressure-flow parameters with finasteride was greater in men with large prostates than in those with smaller prostates (8). In the second study, a modest, but statistically significant, correlation between detrusor pressure and prostate size was found, supporting the hypothesis that prostate size is important in deciding between various medical treatment options for BPH (9). Another study by Lepor *et al*. again questioned the efficacy of finasteride in improving the patient’s quality of life, and claimed that baseline prostate volume was not a predictor of response to finasteride. However, the mean prostate volume of the patients included in this trial was less than 40 mL (10).

Two important trials published since 1996 concluded that finasteride significantly reduced acute urinary retention and the need for surgical treatment in men with BPH (11,12). As the reduction in prostatectomy and acute urinary retention rates was rather small, the cost of achieving these results has been questioned (13). The long-term effects of finasteride have also been examined. The North American Finasteride Study Group recently reported that patients treated with finasteride maintained a reduction of prostate volume and an improvement in symptom score and maximal urinary flow rate over 5 years (14). The PROWESS Study Group (15) also found that finasteride caused long-term symptomatic improvement and verified the results of other reports (11,12) discussed above. The risk of developing acute urinary retention or of needing surgery was also found to be reduced (15). In addition, the Scandinavian Finasteride Study Group has verified an earlier observation that the maximum efficacy of finasteride action is obtained after 6 months, and has shown that this improvement could be maintained for at least 6 years (16).

The mechanism through which finasteride accomplishes its long-term effects has also been examined (17). Finasteride was shown to cause progressive contraction of the prostatic epithelium in the peripheral and transition zones, and this contraction was demonstrated to continue for many months after clinical improvement had been established.

The combination of finasteride with an alpha$_1$-blocker has been examined in two clinical trials (5,18); no additional benefit from combining these two drugs was observed in either study.

Another important benefit of finasteride in common clinical urological practice is that it can be used to treat haematuria associated with BPH. Two studies have confirmed this alternative for patients with haematuria due to BPH who, at the same time, had no significant obstruction or adenocarcinoma of the prostate (19,20).

Side-effects: These are mainly related to sexual function. Ejaculation disorders, impotence and decreased libido have been reported in 12% of patients receiving finasteride; these figures were higher than those observed for placebo (7). Such side-effects were considered “minimal” by the World Health Organization (WHO)

Experts Committee during the Fourth International Consultation on BPH in Paris in 1997 as they did not increase over time and did not cause many patients to discontinue their treatment.

Effect on PSA level: It is known that finasteride lowers serum PSA levels; therefore, the question of whether or not it masks the early detection of localized prostatic adenocarcinomas has been raised. Since 1997, it has been agreed that 12 months of finasteride, 5 mg daily, reduces serum PSA levels by 50% (7). Recently, numerous studies have been published addressing this problem. Two major studies (21,22) verified earlier reports and concluded that doubling the PSA level allowed appropriate interpretation of PSA values and that finasteride treatment did not mask the detection of prostatic adenocarcinomas. It was also shown, at the histopathological level, that finasteride did not cause problems in the diagnosis of cancer from needle specimens as cancer tissue remained unaltered (23). However, contradicting all of the above results, are those of a recently published study in which only 35% of men on finasteride showed the expected 40-60% reduction in PSA level, making it difficult to monitor these patients for protate cancer (24).

The results of papers dealing with the impact of finasteride on free PSA level are confusing. In one paper, finasteride seemed to lower total and free PSA levels equally, so that the free PSA-to total-PSA ratio remained unchanged (25). In another report, the percentage of free PSA did not change significantly (26).

### 4.8.2 Phytotherapeutic agents

The use of alternative treatment for BPH with phytotherapeutic agents has been popular in Europe for many years and has recently spread substantially in the USA (27). These agents are composed of various plant extracts and it is always difficult to identify which component has the major biological activity. During the Fourth International Consultation on BPH all the available data on phytotherapy were analysed. Only a few studies were found to have the statistical power and proper follow-up period to prove the clinical efficacy of these agents (28).

A meta-analysis of 18 randomized, controlled trials involving 2,939 men was performed and concluded that *Serenoa repens* produced similar improvements in symptoms and urinary flow to finasteride, with fewer side-effects (29). A recent review re-evaluated all the latest reports and concluded that the efficacy of phytotherapeutic agents has yet to be proven, although a few papers suggest that some benefit from these agents exists (27).

### 4.8.3 Conclusions

- It has been shown in numerous randomized, placebo-controlled clinical trials that finasteride is capable of reducing prostate volume and improving symptom scores and flow rates. Maximum benefits are seen at a mean period of 6 months.
- The clinical improvement seen with finasteride treatment is best validated in men with enlarged prostates (> 40 mL).
- Finasteride can alter the natural history of symptomatic BPH by influencing prostatectomy and acute urinary retention rates. The costs of such protocols, however, should be further evaluated.
- The long-term (up to 6 years) effects of finasteride are substantial.
- The combination of finasteride with an alpha$_1$-blocker is of no benefit to patients according to the data currently available.
- Side-effects of finasteride are minimal.
- Finasteride treatment does not mask the detection of prostate carcinoma. By doubling PSA serum levels an accurate estimation can be expected.
- The mode of action of phytotherapeutic agents is unknown. Their biological effect is unclear, although a few randomized clinical trials already show encouraging results.

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## 4.9 Medical treatment II: alpha-blockers

Over the past 10 years, the prescribing of alpha-blockers has steadily increased. This increase has been driven partly by patients wishing to achieve symptomatic relief without undergoing surgical treatments and partly by the marketing of these drugs by pharmaceutical companies. In view of the very real placebo effect seen in the treatment of patients with LUTS secondary to BPH, this review will focus on the results of randomized, prospective, placebo-controlled clinical studies.

### 4.9.1 Uroselectivity

Alpha-blockers were first introduced into clinical practice for the treatment of LUTS secondary to BPH in 1978, following experimental work demonstrating the predominance of adrenoceptors in human prostate smooth muscle (1). Initially, the non-selective alpha-blocker, phenoxybenzamine, was investigated; however, the side-effect profile due to its unselective nature was unacceptable to patients (2,3). Subsequently, $alpha_1$-adrenoceptors were identified and selective, better-tolerated alpha-blockers were developed. A large number of $alpha_1$-selective, alpha-blockers are available (alfuzosin, doxazosin, indoramin, prazosin, terazosin). Broadly speaking they all have similar efficacy and side-effect profiles. Following the identification of $alpha_1$-adrenoceptor subtypes, a new selective alpha-blocker, tamsulosin, which specifically blocks the $alpha_{1A}$-receptor subtype, has been introduced.

### 4.9.2 Mechanism of action

Alpha-blockers are thought to act by reducing the dynamic element of prostatic obstruction by antagonizing the adrenergic receptors responsible for smooth muscle tone within the prostate and bladder neck. This is implied from in-vitro experiments and the predominant distribution of $alpha_1$-receptors within the prostate and bladder neck. However, the exact contributions of $alpha_1$-receptor subtypes and potential central effects *in vivo* remain unclear. Urodynamic studies measuring voiding pressures do not reveal any significant relief of obstruction, although flow rates do improve with these agents relative to placebo.

### 4.9.3 Pharmacokinetics

Alpha-blockers are taken orally and the dosage depends on the half-life of the relevant drug. Tamsulosin, terazosin and doxazosin have the advantage of being long-acting, once-daily preparations, which is beneficial in terms of compliance. Dose titration is recommended for most alpha-blockers, with the exception of tamsulosin, in order to maximize efficacy and reduce morbidity.

### 4.9.4 Assessment

After basic assessment according to the guidelines described in previous chapters, patients with specific indications for surgery, such as urinary retention, recurrent urinary tract infection, chronic renal impairment and recurrent prostatic bleeding, should be excluded from alpha-blocker therapy. All patients requiring treatment for symptoms alone, who do not fall into these groups, are candidates for medical treatment, and alpha-blocker therapy should be discussed as a treatment option. There are no means of predicting the response to treatment based on symptom scores or flow rates (4). Caution should be exercised when treating patients receiving antihypertensive therapy and those with postural hypotension.

### 4.9.5 Clinical efficacy

The interpretation of existing literature regarding the efficacy of alpha-blocker therapy is clouded by the wide discrepancy in methodology and reporting of clinical studies. It must be remembered that the placebo effect in clinical studies related to BPH can be marked. In three placebo-controlled studies involving doxazosin (5), terazosin (6) and tamsulosin (7), the respective improvements in symptom scores with placebo were 8%, 10% and 8%, respectively, and improvements in flow rate were 7.1%, 8.3% and 3.8%, respectively. Hansen *et al.* reported a statistically significant reduction of 24% in symptom score and an increase of 14% in flow rate following 16 weeks of placebo treatment (8).

A large number of randomized, placebo-controlled studies report the clinical efficacy of selective alpha$_1$-blockers, and these have been comprehensively reviewed by Chapple *et al*. in the Fourth International Consultation on BPH (9). These studies confirm significant differences compared with placebo, with symptom scores reduced by 20-50% and flow rates improved by 20-30%. In a patient with reduced flow, an improvement of 20-30% may represent a modest change of as little as 2-3 mL/s. The review concentrated on alfuzosin, terazosin, doxazosin and tamsulosin; however, earlier alpha-blockers, such as prazosin and indoramin, result in similar improvements in flow rates and symptoms. Symptomatic improvement is noted within 48 hours and is durable, with significant improvements maintained for up to 42 months. Very few studies include quality-of-life data, but those that are available show a good correlation between symptom scores and quality-of-life scores (10).

There is no significant difference in terms of clinical efficacy between different alpha-blockers in the small numbers of comparative clinical studies published. Buzelin *et al*. (11,12) compared prazosin and alfuzosin, as well as tamsulosin and alfuzosin, in separate randomized clinical trials. There was no difference in clinical efficacy with these agents, and the number of adverse events was too small for meaningful statistical analysis.

### 4.9.6 Durability

Durability of treatment is an important economic issue and has been addressed in a number of studies. Unfortunately, these long-term studies were non-randomized and, in many cases, there was a high fall-out rate. Studies with the longest duration of follow-up relate to alfuzosin (13), doxazosin (14), terazosin (6) and tamsulosin (15), and demonstrate sustained improvements in symptoms and flow rates. Patients who discontinue alpha-blocker therapy due to side-effects are likely to do so within the first 8 weeks.

### 4.9.7 Adverse effects

The most commonly reported side-effects with alpha-blocker therapy are headaches, dizziness, postural hypotension, asthenia, drowsiness, nasal congestion and retrograde ejaculation. The incidence of side-effects in relation to individual alpha-blockers has been comprehensively reviewed by Chapple *et al*. in the Fourth International Consultation on BPH (9). In many studies, the incidence of side-effects is similar to that of placebo; while in others it can be as high as 20%. Although it is claimed that the side-effect profile of the alpha$_{1A}$-selective blocker is less than that of alpha$_1$-blockers, the clinical data reported are insufficient for meaningful analysis.

### 4.9.8 Combination therapy

Two major studies have looked at the benefits of combining an alpha-blocker with a 5-alpha-reductase inhibitor in patients with clinical BPH (15,16). Neither the Veterans study nor the ALFIN study showed any benefit from combining both drugs, and in both studies the alpha-blocker proved more effective than the 5-alpha-reductase inhibitor.

### 4.9.9 Acute urinary retention

The administration of an alpha-blocker prior to removal of the catheter is advocated in some centres following reports that an increased proportion of patients void successfully (17). However, there are no randomized follow-up data to establish whether patients who void successfully benefit from long-term alpha-blocker therapy or subsequently develop retention requiring surgery.

### 4.9.10 Conclusions

- Alpha-blocker therapy can result in a rapid improvement in symptoms by a factor of 20-50% and an improvement in flow rate of 20-30%. These changes have been shown to be significant in randomized, placebo-controlled studies.
- Long-term data are limited but suggest that the benefits of treatment are sustained. If a patient does not experience an improvement in symptoms after an 8-week trial, treatment should be discontinued.
- Patients should be informed about the side-effects of alpha-blocker therapy and the need for long-term use.
- There does not appear to be a role for alpha-blockers in combination therapy with 5-alpha-reductase inhibitors.
- There is no difference between different alpha-blockers in terms of efficacy. Although the side-effect profiles for some drugs are reported to be more favourable, supportive data are weak. The main differences between alpha-blockers lie in their pharmacokinetic properties and economic cost.

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## 4.10 Surgical management

TURP, TUIP and open prostatectomy (adenoma enucleation through a suprapubic transvesical or a retropubic approach, with perineal prostatectomy being less used) are the three surgical options for the treatment of BPH. Surgical techniques have been described in detail in numerous textbooks and will not be included in this report (1-3).

### 4.10.1 Indications for surgery

The most frequent reason for surgery in BPH is bothersome symptoms refractory to medical treatment (4,5) (Table 5). The citation of 'symptoms of prostatism only' as the only identifiable indication for surgery has increased from 29.5% in the mid-1980's to 80.9% during the 1990's. The reduction in the number of patients with complicated BPH over the last 10 years is probably the result of improved management of this disease, related to better public awareness (5). Complications of BPH are absolute indications for surgery:

- Refractory urinary retention
- Recurrent urinary tract infection
- Recurrent haematuria
- Renal insufficiency
- Bladder stone.

**Table 5. Indications for TURP. Adepted from Mebust *et al*. (4) and Borboroglu *et al*. (5).**

| Indications for surgery | Mebust *et al*. (4) mid-1980's | Borboroglu *et al*. (5) 1990's | p value |
|---|---|---|---|
| No. of patients | 3,885 | 520 | |
| Symptoms of prostatism | 3,522 (90.7%) | | |
| Significant residual urine volume | 1,336 (34.4%) | | |
| Urinary retention, acute | 1,053 (27.1%) | 79 (15.2%) | < 0.001 |
| Recurrent urinary tract infection | 479 (12.3%) | 54 (10.4%) | 0.177 |
| Haematuria | 465 (12.0%) | 23 (4.4%) | < 0.001 |
| Altered urodynamic function | 385 (9.9%) | | |
| Renal insufficiency | 176 (4.5%) | | |
| Bladder stones | 116 (3.0%) | 31 (6.0%) | 0.001 |
| Symptoms of prostatism only | 1,145 (29.5%) | 421 (81.0%) | < 0.001 |
| Prostatism and residual urine | 577 (14.9%) | | |
| Prostatism and acute retention | 372 (9.6%) | | |
| Prostatism and acute retention and residual urine | 217 (5.6%) | | |

Increased post-void residual urine volume may be used as an indication for surgery. However, there is great variability in its measurement and there is no validated information to suggest an upper limit requiring action to avoid irreversible damage to the bladder.

### 4.10.2 Choice of surgical technique

For small prostates of less than 20 g of resectable tissue, TUIP and TURP have a similar impact on relieving obstruction. TUIP carries a lower risk of retrograde ejaculation (0-37% vs. 50-95% with TURP), but does not allow

pathological analysis of the prostatic tissue. Therefore, TUIP may be recommended for patients with a small gland (< 20 g), no median lobe and a low risk of associated prostatic carcinoma (normal DRE and PSA level) (6).

TURP is performed in approximately 95% of surgical procedures. It is recommended if the resectionist believes that the procedure can be completed in less than 60 minutes. The risk of peri-operative TURP complications, including haemorrhage and extravasation, increases with the duration of the operation, which, in turn, is related to the weight of the prostate (6). Open surgery is recommended for large glands, complicated BPH associated with a large bladder stone not amenable to endoscopic lithotripsy, or the need for surgical removal of large bladder diverticula (1).

### 4.10.3 Anaesthesia and peri-operative antibiotics

All three surgical procedures (TUIP, TURP and open prostatectomy) can be performed under either general or spinal/epidural anaesthesia. Local anaesthesia, achieved by transurethral lidocaine instillation and or injection of local anaesthetic into the area of the bladder neck, can be used to perform TUIP or TURP in selected patient with a prostate size of less than 40 g (7,8).

Urinary tract infection should be treated before surgery. The use of prophylactic antibiotics remains controversial; however, it is recommended that patients are given a single systemic dose of antibiotic (first-generation cephalosporin) at the time of initiation of surgery.

### 4.10.4 Treatment outcome

Symptom improvement: All three surgical interventions give the patient a mean probability of symptomatic improvement of over 80%, with open prostatectomy producing a slightly superior outcome. This difference may be related to patient selection bias as there is no direct randomized, prospective study comparing open surgery and TURP (1). There is no difference in outcome between TURP and TUIP, and these results are maintained for up to 6 years (9).

When expressing the magnitude of the improvement as a drop in symptom severity score normalized to 100%, the interventions achieve a drop from baseline of 73%, 79% and 85%, respectively, for TUIP, open prostatectomy and TURP (1). All of the surgical options lower the symptom score to about 10% of the total achievable score, i.e. 3.5 points with the AUA symptom score (1). The difference between the mean pre- and post-treatment scores are, respectively, 43%, 35% and 52% for open surgery, TUIP, and TURP (1).

A recent prospective study performed in France in 631 patients (78% TURP, mean weight 25 g; 4% TUIP 18% open surgery, mean weight 67 g) showed that at 2 years 85% had a normal I-PSS, with a satisfaction index assessed by the urologist or the patient of 93% (10). More recently, a retrospective study conducted in 520 consecutive patients who underwent TURP between 1991 and 1998 at a single institution confirmed these good results, showing a decrease in symptom score (I-PSS) from 23.8 to 6.4, with an average follow-up of 42 months (6-84) (5).

Urinary flow rate: The mean peak flow rate increases from 8.2 to 22.6 mL/s after open prostatectomy, from 7.8 to 15.6 mL/s after TUIP, and from 7.8 to 17.6 mL/s after TURP (1). The percentage change from baseline was +175% after open prostatectomy, +100% after TUIP, and +125% after TURP. The apparently more favourable clinical course for open surgery can be explained by the fact that adenomatous tissue ablation may be more complete after open surgery than after TURP. Residual hyperplastic tissue may be found at the anterior aspect of the prostate and beside the verumontanum (6).

Post-void residual urine volume: All treatment modalities allow a reduction in the post-void residual urine volume of more than 50%: -55% after TUIP, -64% after open prostatectomy and -74% after TURP (1). However, no direct comparison could be made between these three treatment modalities because of a discrepancy between the post-void residual urine volume at baseline evaluation.

### 4.10.5 Bladder catheter duration and hospital stay

Recent data give a mean indwelling urethral catheter time and duration of hospital stay of less than 2 days after TURP (5). The mean length of hospital stay after open surgery varies from 5 to 10 days (11,12).

### 4.10.6 Peri-operative complications

Peri-operative mortality: The risk of peri-operative death is approximately 1.18% and is related to co-morbidity (5). The causes of death are mainly cardiac diseases or pulmonary complications. Mortality rates are identical for TURP and open prostatectomy (13). Recent reports show a clear reduction in mortality risk following TURP; between 1984 and 1990, mortality rates decreased from 1.2 to 0.77% (14). There were no deaths among 520 consecutive patients treated between 1991 and 1998 despite an associated co-morbidity in 30% of the patients (two or more co-morbid disease processes) (5).

Perioperative morbidity:

(a) Transurethral resection syndrome - This is characterized by mental confusion, nausea, vomiting, hypertension, bradycardia and visual disturbance. The symptoms are probably related to fluid reabsorption during the procedure. Symptoms appear when sodium concentration reaches 125 mEq/mL. The risk is proportionally increased with the duration of TURP as it has been estimated that approximately 20 mL/min of irrigation fluid is absorbed by the patient during resection (15). The overall risk of transurethral resection syndrome is estimated to be 2% (4). Treatment is based on diuretic (furosemide) administration.

(b) General peri-operative complications - Overall, the risk of developing surgical complications, including pneumonia, deep venous thrombosis, pulmonary embolism, pubic osteitis and wound complications, varies, with estimates from 12% for TUIP to 15% for TURP and 21% for open surgery (1). A retrospective study of patients over 80 years old who underwent transvesical prostatectomy estimated the risk of pneumonia to be 4% and that of deep venous thrombosis to be 2% (12). Wound infection and wound complications are encountered in approximately 3% of open cases (12,16).

(c) Bleeding and the need for blood transfusion - The contemporary estimated need for blood transfusion ranges from 1% for TURP (10) to 4.6% for open surgery (16). The requirement for secondary intervention for bleeding and clot retention ranges from 0.5% for TURP to 2.2% for open surgery (1).

(d) Infectious post-operative complications, i.e. epididymitis and urinary tract infection - The mean probability of developing epididymitis ranges from 1.1% for TURP to 2.6% for open surgery, and the risk of urinary tract infection from 13.4% for open surgery to 15.5% for TURP (1).

### 4.10.7 Long-term complications

Incontinence: The median probability for developing stress incontinence ranges from 1.8% for TUIP to 1.9% for open surgery and 2.2% for TURP (1). The rate of total incontinence is significantly higher for TURP (1.0%) than for TUIP (0.1%) or open surgery (0.5%) (1). It is likely that damage to the sphincter mechanism due to an uncontrolled apical resection may explain the difference between the three procedures.

Bladder neck contracture and urethral stenosis: Overall, the risk of developing a urethral stricture is 2.6% after open surgery, 3.1% after TURP and 1.7% after TUIP. The risk of bladder neck contracture is 1.7% after TURP, 0.4% after TUIP, and 1.8% after open surgery (1).

Impact on sexual function: Apart from the procedure itself, many factors may account for potency disturbance after prostatic surgery.

- Potency: Data on potency after prostatic surgery vary from one study to an another. The overall estimated risk of impotence is 4.6% after TUIP, 13% after TURP and 15% after open surgery (1).
- Retrograde ejaculation resulting from the destruction of the bladder neck is reported in 39% of patients after TUIP, 70% after TURP, and 80% after open surgery (1).

### 4.10.8 Long-term outcome

A favourable outcome is common after surgery: 95% of the patients are unobstructed and subjectively satisfied with their urinary status 5 years after surgery (13).

Long-term risk of mortality: the possibility of an increased long-term risk of mortality after TURP compared with open surgery has been raised by Roos *et al*. (17). This issue remains controversial, as since Roos *et al*. no other authors have produced supportive evidence that TURP results in higher long-term mortality rates than open surgery (18).

Retreatment rate: An additional prostatic operation is reported at a constant rate of approximately 2% per year (17). This includes re-operation for bladder neck contracture and urethral stricture. A second TURP for BPH only is reported in 5.5% of cases over a period of 6 years (14). The risk of re-operation for BPH after open surgery is lower.

### 4.10.9 Cost of treatment

A comparative analysis of the estimated cost of medical treatment and surgery has been made in France. The mean cost of surgery is US$ 8,500. After 8 years, medical therapy (US$ 960 yearly) becomes more expensive than surgery (10).

### 4.10.10 Conclusions

- Surgical management of the prostate results in significant objective and subjective improvements.
- TUIP should be performed for small prostates, TURP for moderately enlarged prostates and open prostatectomy for severely enlarged prostates.
- The number of patients experiencing complications and morbidity has reduced during the past decade.

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## 4.11 Lasers

The use of lasers to treat BPH has been contemplated since 1986 but was anecdotal until the early 1990's (1,2), when Shanberg et al. (3) reported the use of the Nd:YAG laser to perform prostatectomy in 10 patients with BPH, resulting in marked improvement in their voiding symptoms. With the development of the right-angle fibre and the refinement of both equipment and technique, the results of many studies have been published. However, as far as durability is concerned, long-term follow-up results are only available from initial studies.

### 4.11.1 Laser types

Four types of laser have been used to treat the prostate: Nd:YAG, Holmium:YAG, KTP:YAG and diode. Energy can be delivered through a bare fibre, right-angle fibre or interstitial fibre. The use of contact lasers using a bare fibre has been abandoned. In addition, energy levels can be varied to achieve coagulation or vaporization. The difference between coagulation and vaporization is that coagulation causes little vaporization and depends on temperature changes to achieve permanent tissue damage. There is also secondary tissue slough, which is associated with tissue oedema. Vaporization depends upon temperature changes of over 100°C, which cause the tissue to be dehydrated (4,5). This effect decreases forward scatter into tissue and may cause less tissue oedema. Interstitial treatments depend on inserting the fibre into the prostatic tissue and the use of coagulation techniques (6).

### 4.11.2 Right-angle fibres

From 1991, reports describing a TRUS-guided, side-firing Nd:YAG laser instrument (the TULIP™ device) for BPH therapy appeared in the urological literature (7,8). These and other reports documented the fact that prostatic tissue ablation could be achieved using the Nd:YAG laser. In subsequent years, the TULIP™ device was abandoned and other authors experimented with even greater prostatic tissue ablation using a much simpler side-firing Nd:YAG laser delivery system. This consisted of a gold-plated mirror affixed to the distal end of a standard, flexible, silica-glass, laser transmission fibre (Urolase™ fibre) (9).

Operative technique: Side-firing laser prostatectomy is performed using Nd:YAG laser light at 1064 nm and relatively high power settings (typically between 40 and 80 W), delivered via an optical fibre equipped with a distal reflecting mechanism. This fibre fits through standard cystoscopes and all laser applications are performed transurethrally under the direct visual control of the surgeon. The operation may be performed under general or regional anaesthesia, or under local peri-prostatic block as described by Leach *et al*. (10). The operating time is approximately 45 minutes or less. Optimal tissue ablation is achieved using long-duration (60-90 s) Nd:YAG laser applications to fixed spots along the prostatic urethra. These laser applications are repeated systematically and with considerable overlap until all visible obstructing prostatic tissue has been coagulated (11).

Outcome, morbidity, durability and limitations: There have been many studies comparing side-fire laser to TURP. If randomized studies are considered, the results are quite similar, showing an equivalent improvement in symptom scores and increases in uroflow rates in both groups, although they are higher in the TURP arms (12-17).

An improvement in voiding produced by side-firing Nd:YAG laser prostatectomy has been extensively documented in the urological literature. Kabalin *et al*. (18) reported that 85% of men undergoing laser prostatectomy could expect at least a 50% improvement in either prostate symptom score or peak urinary flow rate. As far as complex urodynamic evaluation is concerned, several studies have demonstrated the ability of side-firing laser prostatectomy to produce a significant improvement in bladder outflow obstruction. Results of pressure-flow studies have been reported by several authors (8,19-21). These authors reported that 78.6-95% of men undergoing laser treatment were rendered unobstructed at 3- or 6-months post-operative follow-up.

Catheter irrigation is generally not required and blood loss is statistically lower with Nd:YAG laser coagulation than with TURP because of the excellent haemostasis produced. Both the US and UK multicentre trials documented dramatic differences in serious treatment-related complications, favouring laser prostatectomy as a much safer procedure than TURP (12,13). Disadvantages are the delayed time to normal voiding and severe dysuria (8,12,22).

In a single-institution, randomized, prospective evaluation, Costello *et al*. (14) found equivalent voiding outcomes for the two procedures, but again documented differences in morbidity between these operations. During the 3-year post-operative follow-up, serious treatment-related complications occurred in 11.8% of laser prostatectomy patients vs. 35.1% of TURP patients. No study has reported any occurrence of impotence or

sustained incontinence. Retrograde ejaculation has been reported in up to 22% of patients. With regard to durability, the observed retreatment rates following laser prostatectomy - approximately 2% per year of follow-up - seem comparable to documented reoperation rates after TURP (18).

Conversely, an Italian retrospective study of 36 patients submitted to side-fire Nd:YAG laser prostatectomy with a minimum follow-up of 5 years reported striking results (23). All patients had undergone pressure-flow studies at 3 months after laser treatment: 32 previously obstructed patients were unobstructed. After 5 years, 43.8% of these patients underwent TURP because of recurring obstruction. Such a retreatment rate is definitely greater than that observed after TURP and even after TUIP. These data therefore suggest caution in giving indications to laser treatment, particularly in patients who are candidates for TURP or TUIP. In fact, these techniques, TURP and TUIP offer better long-term results and comparable (if not superior) efficacy than laser prostatectomy. Further long-term follow-up studies are needed.

The major limitation of the laser technique compared with conventional TURP is the lack of immediate effect and requirement for urinary catheter drainage for several post-operative days. Some patients may require catheterization for 3-4 weeks or more (24). Even after catheter removal, an improvement in voiding occurs only gradually, and most patients do not notice significant benefits until approximately 3-4 weeks post-operatively.

The best results are obtained if the weight of the gland is below 50-60 g; in larger glands significant amounts of obstructive prostatic tissue can be left behind (17). Moreover, men with chronic urinary tract infections and chronic bacterial prostatitis are not good candidates for Nd:YAG laser coagulation of the prostate (18) because of the possibility of infection of the necrotic tissue that remains *in situ* for several weeks after the operation; emergent TURP has been reported to solve this problem (8).

### 4.11.3 ILC

ILC as a therapy for BPH was first mentioned by Hofstetter in 1991 (25). Since then, several variations and technical and procedural developments have been introduced and tested in clinical trials (26). The objective of ILC of BPH is to achieve marked volume reduction and to decrease urethral obstruction and symptoms. Coagulation necrosis is generated within the adenoma, sparing its urethral surface. As the applicator can be inserted as deeply and as often as necessary, it is possible to coagulate any amount of tissue at any desired location. Post-procedure, the intraprostatic lesions result in secondary atrophy and regression of the prostate lobes rather than sloughing of necrotic tissue (27).

Operative technique: Fibres employed for ILC must emit laser radiation at a relatively low power density. The most commonly used fibres are ITT Light Guide™, Dornier, and the Diffusor-Tip™, Indigo. Nd:YAG lasers or diode lasers are used for ILC. ILC can be carried out using the transurethral approach, with local, regional or systemic anaesthesia. The laser fibre is introduced from a cystoscope within the urethra. The total number of fibre placements is dictated by the total prostate volume and configuration. As a general guideline, one or two placements are used for each estimated 5-10 $cm^3$ of prostate volume. In general, the sites for fibre placement are chosen according to where the bulk of hyperplastic tissue is found (26).

Outcome, morbidity, durability and limitations: Studies were performed to compare the results with ILC with those of other laser techniques, primarily TURP. The results of several studies indicated the effectiveness of ILC in treating BPH with regard to symptoms, obstruction and enlargement. All studies reported marked improvements in symptom score, peak flow rate, residual urine volume and prostate volume (26-31). Urodynamic parameters were also measured before and after ILC treatment (32,33). Pressure-flow studies demonstrated a sufficient decrease of the intravesical pressure, urethral opening pressure and urethral resistance.

Prospective and randomized studies were also performed to compare the results achieved with ILC with those of other laser techniques (33) and TURP (30,34,35). Muschter *et al*. reported on a series of 97 patients with severely symptomatic BPH; 48 patients received ILC and 49 underwent TURP (34). Within 12 months, there were no statistical differences between groups for all the considered parameters. However, four ILC patients (8.3%) were considered to be treatment failures and underwent TURP.

As for morbidity, there is a temporary increase of obstruction after ILC, which can result in urinary retention and temporary irritative symptoms, such as urgency (25). Post-operative irritative symptoms have been observed in 5-15% of patients (28,31,34). Post-operative catheterization was required for an average of up to 18 days, although the catheter was removed within 10 days in more than 70% of cases. No study has reported any occurrence of impotence or sustained incontinence, though retrograde ejaculation was occasionally reported, with an incidence ranging from 0-11.9%. Urethral strictures or bladder neck strictures are not common, and have been reported in approximately 5% of patients.

The retreatment rate is up to 15.4% with a maximum follow-up of 12 months; although as follow-up becomes longer, the retreatment rate is expected to be higher. Currently, the results of only one long-term follow-up study are available (36). In 394 patients followed for up to 3 years, the retreatment rate was 3.1% per

year in the first year, rising to 9.6% thereafter (36).

ILC can be performed in small prostates and also seems to be suitable to debulk larger prostates or to treat highly obstructed patients (26). This procedure can be seen as a true alternative to TURP in selected patients with some advantages, such as almost no serious morbidity, and certain disadvantages, such as the need for longer post-operative catheterization and the lack of tissue for biopsy. However, further comparative randomized studies with longer follow-up are needed to assess the durability of this procedure.

### 4.11.4 Holmium laser resection of the prostate (HoLRP)

The Holmium laser (2140 nm) is a pulsed solid-state laser that has been used in urology for a variety of endourological applications in soft tissues and for the disintegration of urinary calculi (37). Prostatectomy using this energy source is a relatively new technique with the first patient reports appearing in 1995 (37,38). The Ho:YAG wavelength is strongly absorbed by water and the zone of coagulation necrosis in tissue is limited to 3-4 mm, sufficient to obtain adequate haemostasis (38). The peak power achieved results in intense tissue vaporization and in precise and efficient cutting ability in the prostatic tissue.

Operative technique: Instrumentation for this technique includes a 550-µm end-firing quartz fibre and an 80 W Ho:YAG laser. A continuous flow resectoscope is required with a working element; normal saline is used as the irrigant. The basic principle of the technique consists of retrograde enucleation of the prostate and fragmentation of the enucleated tissue to allow its elimination through the operating channel of the resectoscope (38,39).

Outcome, morbidity, durability and limitations: As this technique is relatively new, only a few studies with a short follow-up have been published to date. Gilling *et al*. (40) presented the results of a prospective, randomized trial comparing TURP with HoLRP; so far, 120 patients with urodynamic obstruction have been enrolled with prostates less than 100 g in size (Schafer grade 2). Preliminary analysis has revealed a longer mean resection time (42.1 vs. 25.8 minutes; $p < 0.0001$) for HoLRP patients, but a shorter mean catheter time (20.0 vs. 37.2 hours; $p < 0.0001$) and length of hospital stay (26.4 vs. 47.4 hours; $p < 0.0001$). Symptomatic and urodynamic improvement were equivalent in the two groups.

Comparative studies of Nd:YAG vs. prostatectomy have been conducted, clearly demonstrating that HoLRP is associated with significantly shorter catheter time and a lower incidence of post-operative dysuria (41). Unfortunately, the longest available follow-up is only 12 months, which has confirmed the short-term durability of the procedure (36).

Post-operative dysuria is the most common complication, with an incidence of approximately 10% (38,40,42). No major complication has been described; however, the technique is a surgical procedure that requires significant endoscopic skill and cannot be considered easy to learn. Conversely, there are no specific limitations to the procedure; the size of the prostate that can be treated depends on the experience and patience of the urologist, although the presence of a prostate gland over 100 mL is a relative contraindication in urologists' early experience (38). Patients on anticoagulant medication and those with urinary retention can be safely treated (43). Retrograde ejaculation occurs in 75-80% of patients; no post-operative impotence has been reported (38).

### 4.11.5 Conclusions

Laser prostatectomy should be advised for patients who are:

- Receiving anticoagulant medication
- Unfit for TURP (side-fire or ILC)
- Wanting to maintain ejaculation (side-fire or ILC).

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## 4.12 Transrectal high-intensity focused ultrasound (HIFU)

### 4.12.1 Assessment

No specific diagnostic work-up prior to transrectal HIFU therapy is necessary. However, the following parameters should be obtained:

- I-PSS, including quality of life
- Free uroflowmetry, including post-void residual urine volume
- Serum PSA
- TRUS
- Pressure-flow study advisable

### 4.12.2 Procedure

A beam of ultrasound can be brought to a tight focus at a selected depth within the body, thus producing a region of high energy density within which tissue can be destroyed without damage to the overlying or intervening structures (1-3). If the site-intensity is set below the tissue cavitation threshold, the predominant therapeutic effect is the induction of heat. This technique is known as high-intensity focused ultrasound (HIFU). The source for HIFU is a piezoceramic transducer, which has the property of changing its thickness in response to an applied voltage (1-3). Theoretically the prostate can be ablated by HIFU via a transabdominal or transrectal route. In clinical use, however, only transrectal HIFU devices are applied for the indication of BPH.

Clinical data are only available for one device, the Sonablate® (1-4). This system uses the same 4.0 MHz transrectal transducer for imaging and therapy. The focal length (2.5-4.0 cm) is dependent upon the crystal used. The site intensity can be varied from 1,260 to 2,200 W/cm$^2$. Within the HIFU beam focus, an ellipsoidal tissue volume approximately 2 mm in diameter and 10 mm in length is destroyed (1-3). In order to create a clinically useful volume of necrosis, a multiplicity of laterally or axially displaced individual lesions is generated by physical movement of the sound head. The histological effect of transrectal HIFU therapy using the Sonablate® on the canine and human prostate has been studied in detail (1-3,5,6).

### 4.12.3 Morbidity/complications

In general, transrectal HIFU is well-tolerated but requires general anaesthesia or heavy intravenous sedation. The most prominent side-effect is prolonged urinary retention, lasting for 3-6 days. Haematospermia for 4-6 weeks is observed in up to 80% of sexually active men, and patients frequently discharge two to three drops of blood prior to micturition for several weeks. Urinary tract infection occurs in around 7% of patients. No cases of urethral strictures, incontinence or the need for blood transfusion have been reported in the literature.

Two severe complications have been reported. In one patient, perforation of the descending colon approximately 50-60 cm above the treatment zone occurred. It was caused by inadvertent overfilling to 500 mL and subsequent rupture of the condom that covered the ultrasound probe. This complication led to reconstruction of the filling apparatus and the probe such that the problem can now be reliably avoided. The second severe complication was a thermolesion of the rectum requiring surgical intervention. This was most likely caused by using an inappropriately high site intensity exceeding 2,300 W/cm$^2$. As a consequence, the maximum site intensity was set at 2,000 W/cm$^2$.

### 4.12.4 Outcome

In June 1992, an international Phase II clinical trial was initiated to evaluate the safety and efficacy of transrectal HIFU therapy for patients with LUTS due to BPH. To date, several hundred patients have been treated with the Sonablate® at various sites. In the initial US series, Bihrle *et al*. (7) reported on experience with 15 patients and a follow-up of 90 days. The Qmax increased from 9.3 mL/s to 14.0 mL/s and the post-void residual urine volume decreased from 154 mL to 123 mL (7). Ebert *et al*. (8) treated 35 patients, eight of whom had urinary retention. The Qmax increased from 7.6 mL/s to 15.2 mL/s after 3 months. Within the same time period, the post-void residual urine volume decreased from 182 mL to 50 mL and the I-PSS from 17.9 to 7.1. The initial report of the study included 50 patients, 20 of whom were followed up for 12 months (5). The Qmax increased from 8.9 (± 4.1) to 12.4 (± 5.6) mL/s (6 months, n = 33) and 13.1 (± 6.5) mL/s (12 months, n = 20). In the same time period, the post-void residual urine volume decreased from 131 (± 120) mL to 48 (± 41) mL at 6 months and to 35 (± 30) mL at 12 months. The AUA symptom score reduced from 24.5 (± 4.7) to 13.4 (± 4.7) at 6 months and to 10.8 (± 2.5) at 12 months (5). Several other sites have confirmed these data (9-11).

### 4.12.5 Urodynamics

The urodynamic effect of transrectal HIFU therapy has been studied by Madersbacher *et al*. (12). Thirty patients underwent urodynamic investigations (pressure-flow study) before and after a mean of 4.5 months following HIFU therapy. Pre-operatively 80% were obstructed and a further 20% were in the intermediate zone according to the Abrams-Griffith nomogram. After therapy, a statistically significant decrease in maximum detrusor

pressure, detrusor pressure at Qmax and linear passive urethral resistance relation can be observed. After HIFU, half of the patients were in the equivocal zone and 13% were clearly unobstructed, yet 37% were still obstructed according to the Abrams-Griffith nomogram. The authors concluded that the capability of transrectal HIFU to reduce bladder outlet obstruction was moderate (12). As a consequence, transrectal HIFU should not be considered for severely obstructed patients or those with an absolute indication for surgery.

### 4.12.6 Quality-of-life and sexual function

There are no reliable data on quality of life after transrectal HIFU except from a study by Schatzl *et al*. (13), who studied in detail the early post-operative morbidity of several less invasive procedures. Similarly, there is little data on sexual function. Haematospermia lasting for a maximum of 4-6 weeks is seen in the majority of sexually active patients. Retrograde ejaculation and erectile dysfunction can be safely avoided, although some patients report a decreased ejaculate volume.

### 4.12.7 Durability

The long-term outcome of 80 patients with a follow-up of up to 4 years and a minimum follow-up of 2 years has been studied (14). The mean follow-up of the study population (excluding patients who crossed over to TURP due to insufficient therapeutic response) was 41.3 months (range 13-48 months). Thirty-five men (43.8%) underwent TURP due to an insufficient therapeutic response during the 4-year study period. The retreatment-free period was significantly longer for patients with a pre-treatment average flow rate of more than 5 mL/s ($p = 0.05$) and lower grades of urodynamically documented bladder outlet obstruction ($p = 0.03$) (14). A similar trend, which did not reach statistical significance, was noted for individuals with a higher Qmax and lower post-void residual urine volume.

### 4.12.8 Patient selection

The fact that only a handful of clinical studies with a limited number of patients have been published, hinders a reliable statement concerning patient selection, yet a few selection criteria have been identified. Patients with one or more of the following criteria are unsuitable for transrectal HIFU therapy:

- Prostates with dense calcifications (possibility of tissue cavitation)
- Large prostates (> 75 mL)
- Rectum to bladder neck distance over 40 mm
- Large middle lobes
- Higher grades of bladder outlet obstruction (BOO) - (higher treatment failure rate)
- Absolute indication for surgery

### 4.12.9 Conclusions

Transrectal HIFU therapy is the only technique that provides non-invasive tissue ablation; however, general anaesthesia or at least heavy intravenous sedation is required. Improvement of urinary symptoms is in the range 50-60% and Qmax increases by a mean of 40-50%. Long-term efficacy is limited, with a treatment failure rate of approximately 10% per year. No data are yet available from randomized, controlled trials.

## 4.13 TUNA®

### 4.13.1 Assessment

No specific diagnostic work-up prior to TUNA®, is necessary, but the following parameters should be obtained:

- I-PSS, including quality of life
- Free uroflowmetry, including post-void residual urine volume
- Serum PSA
- TRUS
- Pressure-flow study (advisable)

### 4.13.2 Procedure

The TUNA® device delivers low-level radio frequency energy to the prostate via needles inserted transurethrally (15,16). The TUNA® catheter is a specifically designed cystoscopic instrument with an outer diameter of 22 fr gauge and 0° lens system. Two needles reside invisibly within the catheter tip, each with its own outer protective Teflon shield (16). When deployed, the needles diverge out at an angle of 40º to each other and at 90º to the catheter's longitudinal axis. The physical properties of radio frequency energy dosimetry studies, TUNA® generator characteristics, histopathology and previously reported clinical data have recently been summarized (16). The results of an immunohistochemical study of human prostates treated by TUNA® prior to resection suggest that the therapeutic effect may be mediated by long-term destruction of alpha-receptors and/or sensory nerves (17). Theoretically, the best locations in which to induce necrotic lesions are submucosal and subcapsular nerve endings (17).

### 4.13.3 Morbidity/complications

TUNA® is usually performed as an out-patient procedure under local anaesthesia, although intravenous sedation is required in some patients (16). Post-operative urinary retention is seen in 13.3-41.6% of patients and lasts for a mean of 1-3 days; within 1 week, 90-95% of patients are catheter-free (16). Transient, self-limiting haematuria is experienced by most patients and the risk of transfusion can safely be avoided. Irritative voiding symptoms lasting up to 4-6 weeks are frequently present (13). Continence status is not affected. Urinary infection and epididymitis occur uncommonly, while urethral strictures occur in 0-1.5% of patients. Little evidence exists that TUNA® induces retrograde ejaculation; however, a marginal decrease in the volume of the ejaculate has been observed.

### 4.13.4 Outcome

Several non-randomized clinical trials have documented the clinical efficacy of this procedure with a fairly consistent outcome (18-21). Worldwide, approximately 650 patients have been studied in strict clinical trials. The symptomatic improvement reported ranged from 40-70%. These data are statistically significantly better than at baseline and clearly surpass the expected placebo effect, which ranges from 20-30%. Improvements in Qmax vary widely from 26-121% in non-retention patients. The decrease in post-void residual urine volume similarly ranges from 13-80%. There is no convincing evidence that prostate size is significantly reduced following TUNA®.

### 4.13.5 Randomized clinical trials

The clinical efficacy of TUNA® compared with TURP has been documented in two trials (22,23). Bruskewitz *et al*. (22) presented 12-month follow-up data. In both treatment arms, there was a significant decrease in AUA symptom score and bother score, although improvements were slightly higher in the TURP arm. Improvement in Qmax was significantly higher after TURP than after TUNA® and the decrease of post-void residual urine volume was comparable for both procedures. Adverse events, such as bleeding, dysuria, erectile dysfunction, urinary tract infection or strictures, were more frequent in the TURP arm (22).
Similar data have been reported by Virdi *et al*. (23) in a study involving 24-month follow-up data. Qmax improved by a mean of 287% after TURP compared with 85% after TUNA®, and the decrease in symptom score was comparable in both treatment arms, 83% after TUNA® and 88% following TURP.

### 4.13.6 Impact on bladder outflow obstruction

The impact of TUNA® on bladder outflow obstruction as assessed by pressure-flow studies was determined in five clinical studies (24-28). In all studies, a statistically significant decrease in maximum detrusor pressure or detrusor pressure at Qmax was demonstrable, yet a number of patients remained in the obstructed range after TUNA® therapy.

### 4.13.7 Durability

Several authors have reported on the long-term efficacy of the TUNA® procedure; within 1 year, positive results can be translated into percentages ranging from 5-42% (16). Schulman et al. (29) recently presented 3-year follow-up data on 49 patients after TUNA®. Improvement in Qmax exceeding 50% was seen in 53% of patients after 36 months, and 10 patients (20%) underwent TURP because of an insufficient therapeutic response (16). Long-term follow-up data exceeding this time period are not yet available.

### 4.13.8 Patient selection

Few selection criteria have been identified. TUNA® is not suitable for patients with the following:

- Prostate volumes exceeding 75 mL
- Isolated bladder neck obstruction
- Metallic implants.

### 4.13.9 Conclusions

TUNA, is a simple and safe technique and can be performed under local anaesthesia in a significant number of patients. It results in an improvement of urinary symptoms in the range 50-60% and Qmax increases by a mean of 50-70%. Clinical efficacy has been proven in randomized, controlled trials, although there is limited evidence of long-term efficacy.

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## 4.14 TUMT

### 4.14.1 Assessment

Diagnostic endoscopy of patients with LUTS is usually considered to be an optional test due to the invasive nature of the procedure, but is essential for patients who are to be treated with TUMT. This is because it is important to identify the presence of an isolated enlarged middle lobe or an insufficient length of the prostatic urethra, as these are exclusion criteria for TUMT.

Pressure-flow studies are considered optional for the assessment of patients with LUTS. However, when reduction of bladder outlet obstruction is the aim of a treatment modality, such studies should be performed both before and after treatment to determine the grade of obstruction. Furthermore, several studies have shown that with TUMT the grade of obstruction appears to be a predictive factor for treatment outcome, and pressure-flow studies should therefore be considered mandatory in the diagnostic work-up of TUMT patients.

### 4.14.2 Procedure

TUMT is a registered trademark of Technomed Medical Systems (France), a company considered to be the pioneer of microwave thermotherapy. To date, tens of thousands of patients worldwide have been treated with the Prostatron®, device. Other thermotherapy devices have also been developed: Prostcare®, (Brucker, France), ProstaLund®, (Lund Systems, Sweden) and Targis®, (Urologix, USA). The majority of data in the literature on thermotherapy has been based on the Prostatron®, device. Initial experience focused on low-energy protocols, but subsequently higher energy levels were used to improve treatment outcomes and response rates.

### 4.14.3 The microwave thermotherapy principle

Microwave thermotherapy devices, in general, consist of a treatment module that contains the microwave generator with a temperature measurement system and a cooling system. A treatment catheter is connected to the module and inserted into the prostatic urethra. A rectal probe is provided for monitoring rectal temperature. All devices are computer-guided with a control console for physician interaction and monitoring of the treatment. The devices use different software protocols and treatment algorithms to regulate optimal energy levels and circulation of the cooling fluid in the catheter. The heat energy is produced by a microwave generator with different microwave frequencies that range from 915 MHz to 1,296 MHz depending on the machine used. The main difference between the devices available is the design of the urethral applicator. Apart from differences in the construction of the catheter, the characteristics of the applicators differ, significantly affecting the heating profile (1,2). The similarity in catheter construction consists of the presence of a microwave antenna

positioned in the tip of the catheter just below the balloon. Fluid channels surrounding the catheter provide urethral cooling. Also incorporated in the catheter are one or more temperature sensors that differ in the way they measure temperature.
The catheter is placed transurethrally into the bladder with the patient usually lying in a supine position. After inflation of the balloon, the catheter is withdrawn until the balloon rests gently on the bladder neck. A rectal probe is then introduced to measure the rectal wall temperature on the anterior side of the rectum. The treatment catheter and rectal probe are connected to the control console and treatment is started by circulating water through the catheter. Depending on the software used with the different devices, the microwave antenna is activated after a predetermined time. Depending also on the treatment algorithm employed, energy levels are raised to a maximum of 60 W or 70 W (Prostasoft® 2.0 'Low Energy TUMT' and Prostasoft®, 2.5 'High Energy TUMT'), or as high as 80 W or a maximum of 100 W (Prostasoft® 3.5, ProstaLund® and Prostcare®,).
Different urethral and rectal temperature levels are predetermined at certain safety levels, depending on the apparatus used. In general, the maximum urethral temperature level is set at 44.5°C and the rectal wall temperature at 42.5-43.5°C; whichever energy level is chosen, the same level is maintained throughout the whole procedure (Targis®, Prostcare®, and ProstaLund®,). Alternatively, energy levels start with stepwise energy increments and are adjusted by rectal and/or urethral temperatures accordingly (Prostasoft®, 2.0 and 2.5). The treatment time is approximately 60-90 minutes. At the end of the treatment period, the urethral probe is removed and the patient is catheterised in case of urinary retention.

### 4.14.4 Morbidity

Morbidity following TUMT is an important issue. Low-energy TUMT is well well-tolerated by patients. The perception of discomfort varies from a mild feeling of perineal warmth and a mild urge to urinate to occasional significant discomfort. Distraction and reassurance are usually sufficient to alleviate this, but momentary interruption of microwave emission may be useful in those with major discomfort. Most patients experience perineal discomfort and urinary urgency for several days after treatment, but not usually for longer. Occasionally, haematuria is noticed. No tissue sloughing occurs and urinary retention is expected in up to 25% of patients (2-10). In these cases, a catheter may be necessary for an average of 7 days.

High-energy treatment is also well well-tolerated, although pain medication needs to be administered to most patients prior to or during therapy. On a trial-and-error basis, 30 mg of MS Contin (Morfine Sulfato) administered 2 hours prior to therapy resulted in an almost complaint-free treatment in the majority of patients. In contrast to the low-energy protocol, urinary retention is usual in patients treated with high-energy TUMT; the average catheterization time is 2 weeks. Only two papers mention erectile dysfunction following thermotherapy (incidence 0.8-5%) (11,12). For patients treated with low-energy protocols, the retrograde ejaculation rate ranges from 0-11%, while for high-energy protocols, this figure increases up to 44%.

*Outcome: objective, subjective and urodynamics*

Low-energy protocols: Several versions of the operating software have been used in clinical trials. The standard operating software for the Prostatron®, is version 2.0, and remarkably similar clinical results have been reported worldwide from several centres (2-4,7,11,13-19). The clinical efficacy of TUMT has been confirmed in several randomized, SHAM-(placebo) controlled studies (7,8,20,21). Symptomatic improvement is significant, with a decrease in Madsen symptom score from around 13 to 4. Changes in objective parameters are less pronounced. The mean increase in Qmax is 3-4 mL/s, representing a mean improvement of approximately 35% over baseline. These improvements are noted from 6 weeks and persist over a period of 5 years (22,23).

In order to evaluate the clinical utility of TUMT, a randomized study comparing it with TURP was performed by Dahlstrand *et al*. (24). This study showed significant improvement after both TUMT and TURP in symptom score, Qmax, post-void residual urine volume and grade of bladder outlet obstruction. Although the decrease in symptom score was more pronounced after TURP (92%) than after TUMT (78%), the observed improvement after TUMT corresponded well with that from other reports of TURP (25,26). Also, the improvement in voiding parameters was significantly more pronounced after TURP than after TUMT at 2 years. Although TUMT seems to have a lesser effect on uroflow than TURP, a favourable aspect of TUMT is its decreased morbidity compared with TURP. (See below for a more extensive discussion of TURP.). It may therefore be concluded that the objective and subjective improvements seen following TURP occur at a different range to those observed following low-energy TUMT. Nonetheless, the improvements noted after low-energy TUMT were significant, and there was no deterioration in the improvements seen in these patients at long-term follow-up.

Interestingly, the results achieved with other available thermotherapy devices show remarkably similar results compared with those of the Prostatron® apparatus despite differences in construction. There appears to be a 35-65% symptomatic improvement at 3 months (27-30). Even the Targis® machine from Urologix (which can be considered a low-energy device) produces a flow improvement comparable to the high-energy protocol (30).

High-energy protocol: The elevation of intraprostatic temperatures, as measured by invasive thermometry during TUMT using version 2.0 operating software, has been shown to correlate broadly with clinical outcome (31). The number of patients achieving a successful outcome, defined as either a significant increase in maximum flow or a decrease in symptoms, was significantly greater in those in whom a higher temperature was achieved (32). Consequently, further modifications of the operating software have been made in recent years to achieve higher intraprostatic temperatures and thus provide greater clinical efficacy. The use of higher temperatures may be the only way to achieve removal of obstruction. Program version 2.0 was modified to provide more power at a maximum of 70 W and a higher rectal (temperature) threshold, leading to fewer treatment interruptions and an increase in energy delivered to the prostate.

The first reports on the application of high-energy levels using Prostasoft®, 2.5 were published by de la Rosette *et al*. (33) and Devonec *et al*. (32) and demonstrated clinically significant improvements. More recently, the European BPH Study Group performed a multicentre study of 116 patients using high-energy TUMT (34). In this study, the mean Madsen score improved from 13.6 at baseline to 5.5 at 26 weeks. The improvement in uroflowmetry was more pronounced in contrast to the low-energy protocol. Qmax improved from 9.6 mL/s at baseline to 14.1 mL/s at 26 weeks of follow-up. These objective and subjective improvements were sustained at 52 weeks.

The improvement in uroflowmetry of this high-energy protocol over the low-energy protocol can be explained by the improved ablative capability. At 3-months of follow-up TRUS identified a prostatic cavity in almost 40% of patients. There appeared to be a good correlation between the presence of a cavity and uroflowmetry improvement (35). The best candidates for this treatment protocol appeared to be patients with moderate-to-severe bladder outlet obstruction, as measured by pressure-flow studies, and those with larger prostates (36).

When evaluating the high-energy protocol, the results should also be compared with those obtained following TURP. One-year follow-up results of a prospective randomized study comparing high-energy TUMT with TURP were reported recently (37). After TURP and thermotherapy, there was a significant improvement in all clinical parameters. At 1 year of follow-up, the symptomatic improvement was 78% in the TURP group versus 68% in the TUMT group, with improvements in free flow being 100% and 69%, respectively. Both groups had showed significant relief of bladder outlet symptoms. No serious complications occurred in either group, but one patient in each group required another treatment. It was concluded that satisfactory results were obtained after both treatments, with improvements observed following high-energy TUMT being in the same range as those seen after TURP.

### 4.14.5 High-intensity-dose protocol

Although the results following high-energy TUMT are excellent, changes to the Prostasoft®, software have recently been reported. It was concluded from clinical experience that a shorter duration of treatment did not alter efficacy or decrease morbidity (36). On a conceptual basis, the so-called Prostasoft®, 3.5 protocol differed significantly from former protocols. First, the principle of stepwise energy increments was abandoned and the treatment was initiated at an 80 W energy level. Second, the urethral temperature feedback system was also abandoned. Energy delivery is now guided by the rectal temperature sensor via a feedback loop. Third, the cooling temperature starts at a lower value (8°C) and is also linked to rectal temperature. Finally, the total treatment duration is shortened to only 30 minutes. This Prostasoft®, 3.5 protocol can therefore be considered to be high-intensity-dose TUMT.

In principle, the whole treatment procedure is not altered and the same device and urethral probes are used. With the new software, no interruptions occur as microwave power is automatically adjusted to maintain a stable rectal temperature. This alteration in the algorithm results in a more effective treatment, without compromising safety parameters. In the high-energy protocol, the initial energy level starts at 20 W, with gradual increments up to 70 W. The approach was based on the effective levels best tolerated by patients, not on scientific evidence. Insufficient heating of the tissue was suggested as one possible reason for treatment failure. Gradual energy increments might cause tissue adaptation to temperature rise, with recruitment of tissue defence systems such as the ‘heat sink’ mechanism. The immediate emission of energy at a higher level results in a ‘heat shock concept’, eliminating these suggested limitations.

In the initial protocol, the treatment duration was set at 1 hour. More recently, however, there has been strong clinical support for reducing the treatment duration (38). The latest Prostasoft® 3.5 protocol is based on a merging of these different concepts, resulting in a high-intensity-dose TUMT treatment.

Initial clinical studies were started in January 1998. Data have been generated from a cohort of 93 patients with a mean age of 66 years and an average prostate volume of 60 $cm^3$. An average total energy of 92 kJ was delivered, while the power emitted averaged 56 W. The majority of patients tolerated the treatment very well, and patient discomfort was comparable to that reported with the former 2.5 protocol, but with a limited treatment duration of 30 minutes. The demographics of this cohort were similar to those of patients in which earlier treatment protocols were assessed. Overall, the results were comparable to those achieved with the 2.5 high-energy protocol.

### 4.14.6 Quality of life and sexual function

The treatment of BPH has been redefined during the last decade because of the extensive investigation of alternative treatments to TURP. Several factors have modified general treatment patterns, including recognition of risk and limitations of prostatectomy, acceptance of medical therapies, development of minimally invasive treatment alternatives, and progress in understanding appropriate indications for intervention. As BPH is rarely a life-threatening condition, therapy aims to improve quality of life by relieving bothersome urinary symptoms. These alternative therapies for BPH have a different impact on changes in quality of life compared with TURP. The demand for minimally invasive medical care by increasing numbers of younger, less symptomatic, and sexually active male patients requires attention.

Relatively little is known about the impact of thermotherapy on quality of life. In a study by Francisca *et al*. (12), changes in quality of life and sexual function were evaluated in a placebo-controlled TUMT study. They found significant improvement in voiding and symptomatic parameters. However, no significant difference in patient acceptance of voiding problems was noticed. This might be explained by the non-disease specificity of the quality-of of-life questionnaire, as no validated questionnaires were available at the time of the study. Furthermore, statistical difference might be different from clinical difference. Finally, symptom score and quality-of of-life questions might measure completely different aspects of the disease.

Another study by Tsang and Garraway (39) demonstrated that the symptoms of BPH were associated with restrictions in activities of daily living, including sleeping, driving, playing outdoor sports and visiting the cinema and theatre. Few BPH research scales take sexual function into account, probably because BPH itself does not influence the sexual functioning of patients. The ICS BPH study revealed that sexual activities are frequently spoiled by voiding problems (40). Sexual function is indeed an essential component of quality of life in male patients. As the majority of patients seeking medical treatment are sexually active, the impact of BPH treatment on sexual function should be integrated into all disease-specific outcome measures.

Data on changes in sexual function with the low-energy TUMT device showed no significant difference to those with placebo and TUMT (12). Sexual function following HE-TUMT was reported on by the same group (41). They concluded that although transurethral resection was more effective than TUMT, both treatment modalities significantly improved clinical outcome. However, high-energy TUMT is a better therapeutic option than surgery for patients who want to preserve sexual function. In particular, erections and ejaculation were preserved more often after TUMT, while there was a significant deterioration of these functions following TURP (41).

### 4.14.7 Durability

The retreatment rate after prostatectomy may reach up to 15% and depends on the follow-up interval. Several studies using low-energy thermotherapy report on surgical re-treatment rates for up to 1 year. At Charing Cross Hospital in London, 100 patients were followed up and, at 1 year, 11% had required TURP for persistent symptoms or high residual urine volume (42). De la Rosette *et al*. (5) presented the results of a group of 130 patients with a follow-up of 1 year; in this group, 8% were additionally treated with TURP. In a study by Dahlstrand *et al*. (24) among 39 patients treated with TUMT, 10% were considered non-responders and underwent TURP. Blute *et al*. (2) published the results of a study of 150 patients with a follow-up of 1 year; 12% were regarded as non-responders. On the other hand, Van Cauwelaert *et al*. (15) and Tubaro *et al*. (18) reported only low retreatment rates with significant subjective and objective improvements.

When applying higher energy levels, the outcome seems improved and may eventually result in a more durable response. In a study by de la Rosette *et al*. (8,33), it appeared that additional TURP was performed in only three out of 116 patients. No bladder neck contraction or urethral strictures were reported. De Wildt *et al*. (43) confirmed these findings, documenting five surgical interventions at 1-year follow-up in 85 patients treated. Dahlstrand *et al*. (24) presented data on 3-year follow-up showing that effects persist for at least 3 years. De Wildt *et al*. (43) published their data on a group of 305 patients treated with low-energy TUMT. After 3 years follow-up, 133 patients had only been treated with TUMT. Over this period of observation, there was a significant symptomatic improvement over baseline (Madsen symptom score, 12.9 to 5.6 at 1 year, 6.8 at 2 years, and 11.7 at 3 years, post-treatment) and improvement in Qmax of 2.6 mL/s. A total of 125 patients were retreated with either invasive or medical treatment. Low-energy TUMT showed a significant and durable improvement in baseline parameters in 51% of patients.

A similar trend was observed in a long-term, follow-up study by US investigators (44). However, in contrast with the European study, a larger number of patients received additional medical treatment and consequently the number of surgical interventions was lower. Few patients (11.1%) underwent surgical intervention despite specific selection of a group of patients who would normally be treated with TURP. The results of TUMT at 4 years show sustained symptomatic improvement (44).

### 4.14.8 Patient selection

Treatment outcome analysis demonstrates a considerable variability in individual response. Some patients do

surprisingly well, while others show almost no response to treatment. In an attempt to provide selection criteria for the low-energy protocol, de Wildt *et al*. (33) analysed the patient profile prior to treatment of a group of responders and non-responders to TUMT. There was no difference in the two patient groups before treatment with regard to age, Madsen symptom score, uroflowmetry performance, post-void residual urine volume or prostate volume. It was concluded that no clinical parameters exist for either prediction of clinical outcome or selection of the ideal candidate when using this treatment protocol.
Alternatively, Arai *et al*. (45) conducted a retrospective analysis and found that patients with apparent obstructive symptoms and with a moderate enlargement of the prostate showed a more favourable response to TUMT. However, this analysis included only 32 patients and follow-up parameters were obtained at 2 months after TUMT.

Using urodynamic studies with pressure-flow analysis, two distinct groups of patients, who respond differently to low-energy thermotherapy (46-48), could be identified. It was hypothesized that if thermotherapy modifies the elasticity of the prostatic urethra, patients suffering from reduced elasticity should be ideal candidates for this treatment modality. Indeed, an analysis of data from a large European multicentre study showed that a certain type of obstruction responded favourably to this therapy (48). Although no significant difference was found between the two groups at baseline with regard to symptoms or uroflow parameters, there were significant differences in changes in objective parameters after treatment. Patients with a predominantly constrictive pattern of obstruction had a significantly greater improvement in both maximum and average flow rates, as well as in decrease in residual urine volume, compared with compressive obstruction.

In a recent study, de la Rosette *et al*. (33,34) showed that HE-TUMT resulted in a significant and substantial decrease of in bladder outlet obstruction. It was concluded that patients with higher grades of bladder outlet obstruction seemed to be better candidates for this treatment. Besides the grade of bladder outlet obstruction, prostate size seems to be an important parameter. Patients with larger prostates also responded best to this treatment protocol (33,34).

The position of these two different treatment protocols with differences in outcome and morbidity in the armamentarium of therapeutic options requires clarification.

- The low-energy protocol, with an excellent subjective response and minimal morbidity, should be recommended in patients with smaller prostates and lower grades of bladder outlet obstruction.
- The high-energy protocol is recommended in patients with larger prostates and higher grades of bladder outlet obstruction. It results in excellent subjective **and** objective response but carries a higher morbidity.

As the morbidity is relatively low for both protocols and the treatment can be performed without anaesthetic; patients in poor health are particularly good candidates for thermotherapy. A group of 47 patients (ASA risk groups III-IV) with a retention were treated according to the high-energy protocol. Good results with regard to catheter release were obtained, with a success rate of 81% in 6 months (C. Chaussy, personal communication).

### 4.14.9 Conclusions

- TUMT produces significant subjective and objective improvement, with sustained and durable long-term results.
- Morbidity after TUMT consists mainly of the need for catheter drainage after treatment due to urinary retention.
- High-energy TUMT is associated with improved objective results compared with low-energy TUMT, but with increased morbidity.
- Newer protocols aim to reduce morbidity and treatment time with sustained objective results and durability.

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## 4.15 RECOMMENDATIONS FOR TREATMENT

- The WW policy should be recommended to patients with mild symptoms that have minimal or no impact on their quality of life.
- Finasteride is an acceptable treatment option for patients with bothersome LUTS and an enlarged prostate (> 40 mL) and can be used when there is no absolute indication for surgical treatment.
- Alpha-blocker therapy is a treatment option for patients with bothersome LUTS, irrespective of prostate volume, who do not have an absolute indication for surgical treatment.
- Surgical management (TURP, TUIP open prostatectomy) is recommended as first-line treatment for patients with (an absolute indication for treatment of) LUTS.
- Significant post-operative morbidity, disappointing long-term data and higher costs have resulted in a substantial decline in the clinical use of side-fire and ILC. It is not recommended as a first-line surgical treatment for patients with LUTS, but side-fire and ILC may have a role in the treatment of high-risk patient subgroups.
- HoLRP is a promising new technique with outcomes in the same range as those of TURP.
- Transrectal HIFU therapy is currently not recommended as a therapeutic option for elderly men with LUTS and is considered an investigational therapy.
- Due to the significant treatment failure rate, TUNA®, is not recommended as a first-line therapy for patients with LUTS.
- TUMT should be reserved for patients who prefer to avoid surgery or who no longer respond favourably to medication.
- Patients with mainly symptomatic BPH without signs of bladder outlet obstruction are the best candidates for low-energy TUMT protocols.
- Patients with higher degrees of obstruction and larger prostates are better candidates for high-energy TUMT.

# 5. FOLLOW-UP

All patients who receive treatment require follow-up, which will depend on the type of treatment modality undertaken. Patients who subsequently develop chronic retention will require evaluation of their upper tract by serum creatinine measurement and/or renal ultrasound. These patients may be candidates for urodynamic assessment and surgical treatment.

## 5.1 Watchful Waiting (WW)

Patients who elect to pursue a WW policy should be reviewed at 6 months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended:

- I-PSS
- Uro-flowmetry and post-void residual urine volume

## 5.2 Alpha-blocker therapy

Patients should be reviewed after the first 6 weeks of therapy in order to determine their response. If patients gain symptomatic relief in the absence of troublesome side-effects, alpha-blocker therapy may be continued. Patients should be reviewed at 6 months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended:

- I-PSS
- Uro-flowmetry and post-void residual urine volume

## 5.3 5-alpha-reductase inhibitors

Patients should be reviewed after 12 weeks and at 6 months to determine their response. Subsequent review is as for alpha-blocker therapy. The following are recommended:

- I-PSS
- Uro-flowmetry and post-void residual urine volume

## 5.4 Surgical management

Following surgical treatment, patients may be seen within 6 weeks to discuss the histological findings and to identify early post-operative morbidity. Long-term follow-up should be scheduled at 3 months to determine the final outcome. Patients who fail treatment should have urodynamic studies with pressure-flow analysis. Assessment includes:

- I-PSS: recommended
- Uro-flowmetry and post-void residual urine volume: recommended
- Urine culture: optional
- Histology: mandatory

## 5.5 Alternative therapies

Long-term follow-up is recommended because of concerns about the efficacy and durability of alternative therapies. The intervals for follow-up will depend on the treatment modality employed. The following time schedule is appropriate for the majority of minimally invasive therapies: within 6 weeks, at 3 months, at 6 months, and then annually. Assessment includes:

- I-PSS: recommended
- Uroflowmetry and post-void residual urine volume: recommended
- Urine culture: optional
- Histology where available: mandatory

## 6. ABBREVIATIONS USED IN THE TEXT

| | |
|---|---|
| AHCPR: | Agency for Health Care Policy and Research |
| ALFIN study: | European multicenter double-blind study to acces The efficacy and safety of Alfuzosin (5mg BID) versus finasteride (5mg OD) and the combination of both in patients with symptomatic BPH. |
| AUA: | American Urological Association |
| BOO: | bladder outlet obstruction |
| BPE: | benign prostatic enlargement |
| BPH: | benign prostatic hyperplasia |
| BUN: | blood urea/nitrogen |
| CT: | computed tomography |
| DAN-PSS: | Danish Prostate Symptom Score |
| dL/dt 40: | velocity of detrusor contraction at 40 mL volume |
| DRE: | digital rectal examination |
| HE-TUMT: | high-energy thermotherapy |
| HIFU: | high-intensity focused ultrasound |
| HoLRP: | Holmium laser resection of the prostate |
| ICS: | International Continence Society |
| I-PSS: | I-Prostate Symptom Score |
| ILC: | interstitial laser coagulation |
| IVP: | intravenous pyelography |
| IVU: | intravenous urography |
| LOCM: | low-osmolar contrast material |
| LinPURR: | Linear Passive Urethral Resistance Relation |
| LUTS: | lower urinary tract symptoms |
| MRI: | magnetic resonance imaging |
| PCAR: | presumed circle area ratio |
| PLESS: | proscar Long-term efficacy and safety stud |
| PPV: | predictive positive value |
| PQSF: | Prostate weight, Quality of life, Symptoms, Maximum flow rate |
| PSA: | prostate-specific antigen |
| Qav: | average flow |
| Qmax: | maximum flow |
| Qm90: | mean flow for middle 90% of voided volume |
| ROC: | Receiver Operating Characteristics |
| VLAP: | visual laser ablation |
| Tdesc: | time from Qmax until 95% of volume voided |
| TRUS: | transrectal ultrasonography |
| TUIP: | transurethral incision of the prostate |
| TUMT: | transurethral microwave therapy |
| TUNA®: | transurethral needle ablation |
| TURP: | transurethral resection of the prostate |
| TUVP: | transurethral electrovaporization |
| URA: | Urethral Resistance Index |
| VLAP: | visual laser ablation |
| WW: | watchful waiting (deferred treatment) |