

# 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 80s (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 40s to 43% in their 60s (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 Is BPH a progressive disorder?

As it is almost impossible to obtain agreement on what it is that defines a man with LUTS/BPH, it seems logical to say that progression cannot be defined in terms of a transition from non-cases to cases. Instead, progression must be measured by documenting deterioration in any number of physiological variables that we associate with the LUTS/BPH syndrome. Traditionally these have included the following:

- decrease in maximum flow rate
- increase in residual volume
- increase in prostate size
- deterioration (increase) in symptom score.

In addition, definable events, such as the occurrence of acute urinary retention or prostate surgery, have been used. Less commonly, changes in urodynamic variables and deterioration in disease-specific quality of life have been advocated. Considerable interest currently rests with PSA. It appears to be as good a predictor of progression as any of the variables mentioned above.

### 1.2.1 Indicators of progression

The strongest evidence to support progression comes from the Olmsted County (20) community-based study and the PLESS placebo group (21).

The strength of evidence for individual parameters as indicators of progression is summarised in Table 1 and is categorised as strong, weak, or none. The actual rates of progression of the individual parameters as determined from the papers reviewed is shown in Table 2. These parameters could potentially be used in decisions about treatment management. Patients who show signs of more pronounced disease progression could be targeted for preventative strategies. The same strategy could be applied to patients who are at increased risk of progression based on recognised risk factors.

Risk factors for progression were found to be age (Olmsted County), PSA (PLESS) and prostate volume (combined 2-year placebo analysis). Other baseline risk factors can be identified, such as symptom severity and decreased urinary flow rate, but current data are not as convincing as those for age, PSA level and prostate volume.

Several other complications, such as renal impairment and bladder dysfunction, have been associated with progression of BPH. Although these are important, they are very rare and therefore could not be evaluated accurately in community-based and clinical studies. The evidence for the progression of BPH has been summarised previously (22).

**Table 1: Strength of evidence for specific parameters as indicators of progression of benign prostatic hyperplasia (BPH)**

	Parameter	Community- based studies	Clinical trials
LUTS	IPSS	S	N/W*
	BII	S	N/N
	QoL	N	W/S*
BPE	DRE	N	N
	TRUS	S	S
	MRI	N	S/S*
BOO	Qmax	S	W/S*
BPH	Histology	N/A	N/A
Miscellaneous	AUR	S	S/S*
	Surgery	S	W/S*
	Crossover/treatment	S	N

\*Conditional risk factors: age and prostate-specific antigen (PSA); S = strong; W = weak; N = no evidence; N/A = not available.

AUR = acute urinary retention; BOO = bladder outlet obstruction; BPE = benign prostatic enlargement; BII = BPH Impact Index; DRE = digital rectal examination; I-PSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; MRI = magnetic resonance imaging; Qmax = maximum flow rate; QoL = quality of life; TRUS = transrectal ultrasonography.

**Table 2: Rates of progression of individual parameters in BPH**

Study	Rate of progression						
	LUTS (points)	Flow rate	Prostate size	Acute urinary retention <sup>a</sup> (Incidence/1000 person years)		Surgery <sup>a</sup> (Incidence/1000 person years)	
				40-49 years	≥ 70 years	40-49 years	≥ 70 years
Olmsted (23-27)	0.18 per year	-2% per year	1.9% per year	3.0	34.7	0.3	10.9
Health Professional (28)	NR	NR	NR	3.3	11.3	NR	NR
PLESS (29)	-1.3 in 4 years <sup>b</sup>	+0.2 mL/s in 4 years <sup>b</sup>	+14% in 4 years	7% over 4 years		10% over 4 years	
2-year studies (30-34)	NR	NR	NR	1.6-4.2% <sup>c</sup> 0.5-3.9% <sup>d</sup>		NR	
North American (35)	NR	NR	NR	NR		10-39% <sup>e</sup>	

<sup>a</sup> Men with moderate to severe symptoms.

<sup>b</sup> Flow rate and LUTS responded to placebo treatment by showing an initial improvement, which deteriorated back towards baseline during the course of the placebo-controlled trial.

<sup>c</sup> According to baseline prostate volume.

<sup>d</sup> According to baseline prostate-specific antigen (PSA) level.

LUTS = lower urinary tract symptoms; NR = not reported.

### 1.2.2 CONCLUSIONS

Based on published data on consequences and complications of the disease, BPH can be considered a progressive disease. There are limited published data on longitudinal studies and the key pieces of evidence that support this notion are the Olmsted County and PLESS studies. A group of patients at increased risk of progression can be identified based on specific risk factors, i.e. age, PSA level and prostate volume. It might be appropriate to identify these patients at risk of progression and initiate early preventative treatment.

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## 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 (1).

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 (2,3).

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 (3).

The only true factors related to the development of the disease are age and hormonal status (4). 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 (5). 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 (6), they still represent the second most common major operation in aged men (7). Ultimately, three in 10 men may undergo surgery for this condition (2).

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% (8,9). 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 (10). For men presenting with urinary retention, the cumulative incidence for prostatectomy is 60% at 1 year and 80% at 7 years (11). 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 (12).

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 (13). 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 (8).

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.

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### 3. ASSESSMENT

Diagnostic investigations have been classified as:

- 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

Probably the best way to assess symptom severity is with a validated symptom score. A number of instruments exist that can measure symptom severity, bother and quality of life (Table 3) (1). Most instruments in current use conform to acceptable standards of validity, reliability and responsiveness; in other words they measure what they

purport to measure, are stable over time and are able to reflect clinically important changes (2).

### 3.1.1 *International Prostate Symptom Score (I-PSS)*

The I-PSS has become the international standard. It is derived from the American Urological Association (AUA) 7 score described by Barry and his colleagues in the early 1990s (3). By adding the scores (with equal weighting) to its constituent questions, a summary or index score is generated which has been shown to be an accurate reflection of a man's overall symptoms over the preceding month (4). The extent to which the self-reported scores reflect actual events has been questioned. Men report nocturia with accuracy but tend to overstate daytime frequency. Correlation of the self-reported score to intermittency or to the strength of stream was poor (5).

Age and cultural factors may be important. The I-PSS appears less reliable in men over 65 years old (6) and careful linguistic validation needs to be undertaken prior to its use in non-North American cultures (7).

Numerous authors have reported and commented upon the poor correlations between I-PSS and other physiological variables. For example, there are numerous reports of symptom severity (as expressed by I-PSS) correlating poorly with peak urinary flow rate, average flow rate, post-void residual volume, prostate size or pressure-flow relationships (1, 8-10). This lack of correlation has troubled many investigators and has led to some questions raised about the validity of the I-PSS. Correlations of similar magnitude have been seen in many other disease areas, e.g. peak respiratory flow correlates poorly with patient's own reports of the severity of their asthma. The lack of correlation can be explained in two ways. Firstly, I-PSS and physiological measures measure different things. Secondly, there are statistical issues related to the clustering of values or data points, which will also result in poor correlation.

A validated symptom score assesses symptom severity. It can be used to monitor change in symptoms over time or following an intervention.

### 3.1.2 *Quality-of-life assessment*

The impact of urinary symptoms on the quality of life is generally evaluated by means of 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. A number of health-related, quality-of-life instruments have been used for clinical research. One of the best known is the generic measure, the Medical Outcomes Study, a 36-item short-form health survey (SF36) (14). It is a self-completed questionnaire used to measure general health status and quality of life. It has been used in a number of studies addressing men with lower urinary tract symptoms. Using this score, a postal population survey among 217 men aged 55 years and over with LUTS showed that, depending on the respondent's 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 a 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.

### 3.1.3 *Symptom score as decision tool for treatment*

Can symptom severity alone be used to allocate treatment? The US Agency for Health Care Policy and Research Guidelines (1) tried to do this. Three categories of symptom severity were described: mild (0-7), moderate (8-19) and severe (20-35). The authors suggested that patients with mild symptoms were most appropriately managed by a watchful waiting approach. Patient with moderate symptoms might benefit from pharmacotherapy, while patients with severe symptoms may derive most benefit from prostatectomy. Although notions of appropriateness have not been well-studied, the proposed policy appears to hold true for patients with mild symptoms but is less reliable for men with moderate or severe symptoms (15).

### 3.1.4 *Symptom score as outcome predictor*

Symptom score may be one of the more powerful predictors of symptomatic outcome (16). As men with mild symptoms have little room for improvement it is of little surprise that they do not experience high levels of symptom reduction following surgery. A man with a pre-operative I-PSS of 17, or more, has an 87% chance of experiencing a substantial symptom reduction (17). There is little evidence that physiological measures improve the chances of predicting a favourable symptomatic outcome.

### 3.1.5 *Conclusions*

Evaluating symptom severity with a symptom score is an important part of the initial assessment of a man. It is helpful in allocating treatment, and in both predicting and monitoring the response to therapy.

### 3.1.6 RECOMMENDATIONS

Recommended investigations:

- Clinical history
- Symptom assessment
- Physical examination
- Validated symptom score, e.g. I-PSS

## 3.2 Prostate-specific antigen (PSA) measurement

Before selecting the proper treatment for men with LUTS, every urologist will perform a DRE and most will measure the serum value of PSA.

### 3.2.1 Factors influencing the serum levels of PSA

In cases where the architecture of the prostatic gland is disrupted, PSA will 'leak' into the circulation. This occurs when prostatic carcinoma is present but also in BPH, prostatitis and after urinary retention. This is why PSA is not considered as being cancer-specific, but organ-specific. Other known causes of PSA serum elevations are biopsy of the prostate gland and ejaculation (1). In addition, small and clinically insignificant changes occur after DRE.

Two other important factors, age and race, must also be considered when evaluating PSA values in men with LUTS (2,3). African-Americans with no evidence of prostate carcinoma have higher PSA values after their fourth decade of life, and therefore age-specific reference ranges must be adapted and interpreted according to race and ethnicity (4). A recent community-based study of African-American men contradicts the beliefs of racial PSA differences, since only minor variations in PSA reference ranges were found (5).

### 3.2.2 PSA and prediction of prostatic volume

Stamey et al. were the first to correlate PSA serum values and volume of prostatic tissue (6). In their studies in the late 1980s, they found that the serum PSA contribution from BPH was 0.30 ng/mL per gram of tissue and 3.5 ng/mL per cm<sup>3</sup> of cancer tissue. Roehrborn et al, have shown that PSA and prostate volume have an age-dependent, log-linear relationship and that PSA has a good predictive value for assessing prostatic volume (7). Vesely et al, also found that prostate volume and serum PSA are significantly correlated and increase with advanced age (8). Prediction of prostate volume can also be based on total and free PSA. Both PSA forms were found to be able to predict the TRUS prostate volume ( $\pm$  20%) in more than 90% of the cases (9).

### 3.2.3 PSA and probability of having prostate cancer

The chance of having prostate cancer is strongly related with the serum value of PSA. For many years the value of 4ng/mL was considered as the upper normal limit of PSA (10) but lately a lower threshold of PSA for recommending prostate biopsy in younger men has shown to improve the clinical value of this test (11).

In order to avoid unnecessary biopsies, Potter et al, (12) have used three clinical parameters - age, PSA and DRE - and have calculated the likelihood of detecting prostate cancer on sextant TRUS-guided biopsies among 2,054 men.

At the same time, predictive nomograms have been developed by various groups. These nomograms are being constructed from variables such as age, race, family history, DRE, PSA, PSA density and TRUS findings (13,14).

### 3.2.4 PSA and prediction of BPH-related outcomes

In a series of studies, Roehrborn et al. (15,16) have shown that PSA and prostatic volume can be used to evaluate the risks of either needing surgery or developing acute urinary retention. These parameters were also related with long-term changes in symptom scores and flow rates. In a recent epidemiological study, elevated free PSA levels could predict clinical BPH, independent of total PSA levels (17).

### 3.2.5 Conclusions

- various factors (cancer, BPH, infection, trauma, age, may influence serum PSA levels
- the level of PSA correlates with the volume of the prostate gland
- the higher the PSA level, the greater is the probability of having prostate cancer
- the PSA level might predict the natural history of BPH.

### 3.2.6 RECOMMENDATION

The measurement of PSA is recommended when a diagnosis of prostatic carcinoma will change the decision made about which therapeutic option to use.



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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 15-30% (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 (blood 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.

*Although the recently released MTOP's data suggest that creatinine measurements might not be indicated, we feel that this study does not address this issue. This study suggests that it is not necessary to control the serum creatinine if voiding is normal.*

#### 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 right men 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 creatinine is highly recommended.

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### 3.4 Urinalysis

Since LUTS is not only observed in patients with BPH, but also frequently in men with urinary tract infections, whether related or not to benign enlargement of the gland, and in at least 25% of patients with carcinoma of the bladder, analytical and microscopic urine analysis was considered to be mandatory.

However, microscopic urine analysis has not been accepted as a screening test for the early detection of severe urological diseases, such as malignancies. This is mainly due to the low specificity of this highly sensitive test, causing unnecessary further diagnostic measures in a large number of patients.

Overall, we concluded that this inexpensive test which does not require sophisticated technical equipment should be incorporated in the primary evaluation of any patient presenting with LUTS.

#### 3.4.1 RECOMMENDATION

Urinalysis is recommended in the primary evaluation. However, it should be noted that there is little evidence in the literature to support this conclusion.

### 3.5 Digital rectal examination (DRE)

Digital rectal examination (DRE) is an important examination in men with LUTS for two reasons. Firstly, it can help to determine the co-existence of prostatic carcinoma. Secondly, it enhances the capacity to estimate prostate volume, and in this way may assist in choosing the right treatment, as prostate size has been shown



to be a determining factor for certain treatment options.

### 3.5.1 DRE and cancer detection

The positive predictive value (PPV) of a suspicious DRE to actually diagnose prostate cancer is 26-34% (1). These figures are based on screening studies and it is believed that DRE will have a higher PPV for cancer among men with LUTS, as these patients are usually older.

Potter et al., used three clinical parameters, age, PSA and DRE, to determine the probability of having prostate cancer and constructed a nomogram to help in the decision whether or not to perform a prostate biopsy. In this study, DRE had a significant influence on the likelihood of a positive biopsy in all PSA and age ranges (2).

In the "Quebec" (3), the "Innsbruck"(4) and the "Olmsted County"(5) screening trials, DRE has been used in the screening process.

In the Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial and in the European Randomized study of Screening for Prostate Cancer in Europe (ERSPC), DRE has been used as an ancillary screening tool. In 1997 the use of DRE in the ERSPC trial as a screening test, was abandoned (6).

In the European Prostate Cancer Detection Study (EPCDS) of 1,051 men, DRE results were not a significant predictor of prostate cancer ( $P=0,21$ ) (7).

### 3.5.2 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 for whom invasive therapy, such as surgery, is recommended, an estimation of the prostate gland volume will help the urologist to select the most suitable form of treatment with the lowest cost and best outcome.

Correct estimation of the prostatic volume by DRE is not an easy task and therefore investigators for the PLCO (Prostate, Lung, Colorectal and Ovarian Cancer) trial have described quality-control procedures for DRE examination (8).

It is well-accepted that TRUS is more accurate in determining prostate volume than DRE. Roehrborn has analyzed the data from four studies in which estimations of prostate volume by DRE were compared with those performed by TRUS (9). Although different methods and criteria were used in 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 predict prostate volume more accurately (10). Similar models to assist training for DRE examinations have been proposed by other groups as well (11).

Finally, Frank et al. have compared the knee-elbow to the left-lateral position of the patient in examining and evaluating the prostate. They concluded that both methods were equal in completeness of examination, pain, and embarrassment (12).

### 3.5.3 CONCLUSIONS AND RECOMMENDATION

1. DRE has been used in all major screening trials but its actual impact in the early diagnosis of PCa has been questioned.
2. DRE is useful in evaluating the size of the prostate gland and also in order to exclude other pelvic pathologies, but proper training is needed.

**Recommendation:** DRE is recommended in the evaluation of men with LUTS.

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### 3.6 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.

#### 3.6.1 Upper urinary tract

A recent survey of 24 urological centres in the UK found 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 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% of IVU and 6.8% of 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 of ultrasonography patients, respectively.

These data need to be correlated with the incidence of renal cell cancer in the general population. Based on 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
- 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.

#### *3.6.2 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 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 bladder wall thickness is currently not part of the recommended diagnostic work-up of patients with LUTS.

#### *3.6.3 Urethra*

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

#### *3.6.4 Prostate*

Imaging of the prostate is performed to assess:

- prostate size
- prostate shape
- occult carcinoma
- tissue characterization.

Choice of imaging modalities

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).

#### *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 benign prostatic enlargement (BPE). In 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 presumed circle area ratio (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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### 3.7 Voiding charts (diaries)

Voiding charts (diaries) are simple to complete and can provide useful and objective clinical information (1,2). There is no standard frequency volume chart available. However, recent data indicate that a 24-hour voiding chart is sufficient and that longer time periods provide only little additional information (3). There is a close correlation between LUTS, as assessed by symptom scores, and data generated by voiding charts, such as frequency and nocturia. The ICS BPH study reported an exact correlation in 41% of the number of voids, 61% for the time of voids and 68% for episodes of nocturia (2). Voiding charts allow, for example, the identification of patients with nocturnal polyuria, one of the causes of nocturia in elderly men (4-6).

#### 3.7.1 CONCLUSIONS

Recording of a 24-hour frequency volume chart in the course of an initial consultation is considered to be a standard investigation. A frequency volume chart is non-invasive, inexpensive, and provides important insights into LUTS.

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### 3.8 Uroflowmetry

Uroflowmetry is recommended as a diagnostic assessment in the work-up of patients with LUTS and is an obligatory test prior to surgical intervention. It is a simple, non-invasive test that can reveal abnormal voiding. Flow rate machinery provides information on voided volume, maximum flow rate ( $Q_{max}$ ), average flow ( $Q_{ave}$ ) and time to  $Q_{max}$ , and this information should be interpreted by the physician to exclude artifacts (1-3). Serial flows (two or more) with a voided volume exceeding 150 mL are recommended to get a representative flow rate. BOO can only be diagnosed with a pressure flow study (pQs) (see section 3.10) and flow rates should be interpreted with caution in particular as elderly men with LUTS have age-related urodynamic changes (4). However, men with a  $Q_{max}$  less than 10 mL/sec are more likely to have BOO and are therefore more likely to improve with surgery. Men with LUTS and normal  $Q_{max}$  are more likely to have a non-BPH-related cause of their symptoms.

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### 3.9 Post-void residual volume

Post-void residual (PVR) urine measurement is recommended during initial assessment. It should be calculated by measurement of the bladder height, width, and length obtained by transabdominal ultrasonography. This is a simple, accurate and non-invasive method. Large PVR volumes (> 200-300 mL) may indicate bladder dysfunction and predict a less favourable response to treatment. Still, residual urine is not a contraindication to watchful waiting or medical therapy. Because of large test-retest variability and lack of outcome studies, it is not possible to establish a PVR “cut-point” for treatment decision.

### 3.10 Urodynamic studies

Pressure-flow studies are regarded as an additional diagnostic test and are considered optional by both the AUA guideline panel on management of benign prostatic hyperplasia (2003) (1) and the Fifth 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 Q<sub>max</sub> of more than 10mL/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. Recent methodological studies looking on intra-individual variation in pressure-flow results as well as intra- and inter-individual observer accuracy in interpretation of pressure-flow curves have demonstrated a considerable methodological variation (3-6).

This makes it more difficult to judge the influence of infravesical obstruction on lower urinary tract symptoms in patients with BPH. 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 (7) and requires 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 (8), Abrams and Griffiths (9) and Rollema and Van Mastrigt (URA – Urethral Resistance Index) (10) are most commonly used, and they all correlate closely. The ICS (International Continence Society) nomogram (11) has now been adopted as the standard nomogram to aid comparison of different data sets, and should be used in clinical practice.

#### 3.10.1 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 LUTS due to BPO relates to TURP. Studies reported by Neal et al. (12,13), Abrams et al. (14), Jensen (15), Robertson et al. (16) and Langen et al. (17) all report improved outcomes in patients who are obstructed prior to surgery, based on pressure-flow studies.

### 3.10.2 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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### 3.11 Endoscopy

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

#### 3.11.1 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 urethrocytostcopy, 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, urethrocytostcopy may provide information about 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.

#### 3.11.2 Morbidity of urethrocytostcopy

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.

#### 3.11.3 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. Urethrocytostcopy 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 appeared to be a trend towards lower peak flow rates in men with higher degrees of trabeculation.

#### 3.11.4 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).

### 3.11.5 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.

### 3.11.6 Relationship between trabeculation and obstruction

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 urethroscopy 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.

### 3.11.7 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 cystography, intravenous pyelography (IVP) or transabdominal sonography, are equally sensitive, or more sensitive, at detecting large bladder diverticula, without carrying the risks of invasive urethroscopy. 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.

### 3.11.8 Bladder stones and obstruction

There is no doubt that the presence of bladder stones can be assessed accurately by urethroscopy. 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 urethroscopy 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.

### 3.11.9 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).

### 3.11.10 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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### 3.12 RECOMMENDATIONS FOR ASSESSMENT

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. Urinalysis may be included in the primary evaluation. However, it should be noted that there is little evidence in the literature to support this conclusion.
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/s, 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. Uroflowmetry is recommended as a diagnostic assessment in the work-up of patients with LUTS and is an obligatory test prior to surgical intervention.
14. Post-void residual urine measurement is recommended during initial assessment.
15. 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.
16. 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.

In straightforward cases presenting for the first time with LUTS, pressure-flow studies remain optional tests.

## 4. TREATMENT

### 4.1 Watchful waiting

Many men with LUTS do not complain of high levels of bother and so are suitable for non-medical non-surgical management - a policy of care that has been called watchful waiting (WW). It is customary for this type of management to include the following components: education, reassurance, periodic monitoring and lifestyle advice. In many men it is regarded as the first tier in the therapeutic cascade and therefore the majority of men will be offered watchful waiting at some point. WW is a viable option to many men as few, if left untreated, will progress to acute urinary retention and complications such as renal insufficiency and stones (1,2). Similarly some men's symptoms may improve spontaneously whilst others remain stable for many years (3).

#### 4.1.1 Patient selection

All men with LUTS should be formally assessed prior to starting any form of management in order to identify those with complications that may benefit from intervention therapy.

Men with mild to moderate uncomplicated LUTS (causing no serious health threat) who are not too bothered by their symptoms are suitable for a trial of WW. A large study comparing WW and TURP in men with moderate symptoms showed that those who had surgery had improved bladder function over the WW group (flow rates and post void residual volumes) with the best results being in those with high levels of bother. 36% crossed over to surgery in 5 years leaving 64% doing well in the WW group (4).

Approximately 85% of men will be stable on WW at 1 year, deteriorating progressively to 65% at 5 years (5,6). The reason why some men deteriorate with WW and others do not is not well understood; increasing symptom bothersomeness and post-void residual volumes appeared to be strongest predictors of failure.

#### 4.1.2 Education, reassurance and periodic monitoring

Although there is little high quality evidence to support this (the studies have not been done) it seems rational to provide the following for men who are candidates for WW:

- prostate, BPH and LUTS education with the help of written information
- reassurance that LUTS does not progress in everyone. Reassurance that serious complications are unlikely to occur.
- information about prostate cancer is nearly always required. Anxiety regarding prostate cancer can be the principal reason why a man consults his doctor about his urinary symptoms. Most men over 50 will note changes in their urinary function with or without high levels of bother. If these men harbour an anxiety about prostate cancer, this may focus their attention on specific symptoms and reinforce their fear. At least three high-quality studies have shown that men with LUTS are at no greater risk of prostate cancer than asymptomatic men of the same age (7-9). It is however not possible to guarantee against early undetectable prostate cancer.
- WW does not imply no activity; men should be periodically seen by either a urologist, general practitioner or specialist nurse. Symptom scores, symptom bothersomeness, flow rates and post-void residual volume measurements are useful in determining whether a patient's condition has deteriorated.

#### 4.1.3 Lifestyle advice

Optimization of WW can be achieved with lifestyle modifications. Minor changes in lifestyle and behaviour can have a beneficial effect on symptoms and may prevent deterioration requiring medical or surgical treatment.

Lifestyle advice should include:

- reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient, for example at night or when going out in public. The recommended total daily fluid intake of 1500 mL should not be reduced.
- avoidance or moderation of caffeine and alcohol which may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency and nocturia.
  - use of relaxed and double-voiding techniques.
  - urethral stripping to prevent postmicturition dribble.
- distraction techniques, such as penile squeeze, breathing exercises, perineal pressure and mental 'tricks' to take the mind off the bladder and toilet in the control of irritative symptoms.
- bladder re-training, by which men are encouraged to 'hold on' when they have sensory urgency to increase their bladder capacity (to around 400 mL) and the time between voids.
- reviewing a man's medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects.
- providing necessary assistance when there is impairment of dexterity, mobility or mental state.



- treatment of constipation.

Again it must be stated that there is little high-quality evidence that provides reliable information on any of these lifestyle activities. Research in this area is required so that lifestyle advice to men with LUTS can be refined.

#### 4.1.4 CONCLUSIONS

Men with mild to moderate LUTS with low levels of bother are suitable for WW. Reassurance, periodic monitoring and lifestyle modifications can be used to optimise WW. Further research in this area is required.

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## 4.2 Medical treatment

### 4.2.1 5-alpha reductase inhibitors

#### 4.2.1.1 Finasteride (type 2, 5-alpha reductase inhibitor)

##### 4.2.1.1.1 Efficacy and clinical endpoints

Today, after the completion of many trials, the efficacy of 5-alpha reductase inhibitors is unquestionable and has been demonstrated over large clinical trials. It 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 the urinary flow rate of 1.3-1.6 mL/s (1-4).

A meta-analysis of six randomized clinical trials showed that baseline prostate volume was a key predictor of various treatment outcomes and that finasteride was more effective in prostates larger than 40 mL (5). Various trials have concluded that finasteride significantly reduced acute urinary retention and the need for surgical treatment in men with BPH (6-8). In a major placebo controlled trial including 3,040 men, finasteride-treated patients had significantly less bother, activity interference and worry due to urinary symptoms. Baseline PSA levels of 1.4 ng/mL, or enlarged prostate glands, could predict the best long-term response to finasteride (9). Data from three multinational, multicentre, placebo-controlled finasteride trials, in 4,222 men, showed that patients with larger prostate volumes or higher PSA levels have an increased risk of developing acute urinary retention and therefore derive the greatest benefit from finasteride therapy (10). The long-term effects of finasteride have also been examined. The North American Finasteride Study Group reported that patients treated with finasteride maintained a reduction of prostate volume and an improvement in symptom score and maximal urinary flow rate over a period of 5 years (11). 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 (12). A recent North American study has also verified that long term (10 year) treatment is well tolerated and results in durable symptom relief (13).

#### *4.2.1.1.2 Haematuria and finasteride*

Another important benefit of finasteride in common clinical urological practice is that it can be used to treat haematuria associated with BPH. Various 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 (14-17).

#### *4.2.1.1.3 Side-effects*

These are mainly related to sexual function. In the PLESS study the side effects reported were decreased libido (6,4%), impotence (8,1%), decreased ejaculate (3,7%) and in less than 1% of the patients other disorders such as rash, breast enlargement and breast tenderness (9). All these figures were higher than those observed for placebo. Such side-effects are considered 'minimal' since they did not increase over time and did not cause many patients to discontinue their treatment. In a recent publication from the PLESS study group it was shown that the finasteride-related sexual adverse experiences occurred mainly during the first year of therapy (18). Another conclusion from the PLESS study was that in both older and younger men with symptomatic BPH, finasteride had the same safety profile and no drug interactions of clinical importance were observed (19).

Finally it has also been shown that the four year inhibition of type 2 5 $\alpha$ -reductase with finasteride does not adversely affect bone mineral density (20).

#### *4.2.1.1.4 Effect on PSA*

It is known that finasteride lowers serum PSA levels. Thus, the question of whether or not it masks the early detection of localized prostatic adenocarcinomas has been raised. It has been agreed that 12 months of finasteride, 5 mg/day, reduces serum PSA levels by 50%. 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).

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 ratio of free PSA to total PSA remained unchanged (24). In another report, the percentage of free PSA did not change significantly (25).

#### *4.2.1.2 Dutasteride*

It is known that finasteride suppresses dihydrotestosterone (DHT) by about 70% in the serum and by 90% in the prostate. The remaining DHT is the result of type 1 5- $\alpha$  reductase activity.

Dutasteride is a new drug that has the ability to suppress both type 1 and type 2 isoenzymes and as a consequence serum DHT decreases by about 90% (26).

A phase II study including 399 patients showed that dutasteride can cause greater suppression of DHT than finasteride (27).

The results of four large randomized, double-blind clinical trials have been presented (28,29). Three of these studies were placebo controlled studies and they showed that dutasteride can reduce prostatic volume by almost 26%, improve symptoms and urinary flow rate and reduces also the incidence of acute urinary retention and BPH related surgery. The fourth compared dutasteride with finasteride for one year which showed that drug related adverse events were similar for both compounds. Pooled data from the patients enrolled in all four studies proved that dutasteride is well tolerated and adverse events included erectile dysfunction, ejaculatory disorders and gynecomastia (28). In a recently published study it was also shown that dutasteride

is associated with clinically significant improvement in BPH specific health status as measured by the BPH Impact Index (BII) (30). Dutasteride shows similar efficacy and tolerability as finasteride in suppressing both type 1 and type 2 isoenzymes but further randomized studies are needed.

#### 4.2.1.3 Combination therapy

The combination of finasteride with an alpha-blocker was examined earlier in two clinical trials (31,32). No additional benefit from combining these two drugs was observed in either study. The lack of finasteride efficacy in these two trials may be due to smaller baseline prostate volumes.

Recently the results of a multicentre randomized, placebo-controlled double-blinded trial (MTOPS trial), have shown that the combination of finasteride to doxazosin was beneficial (33). The combination therapy was superior to either drug alone in reducing AUA symptom scores, in increasing median maximal flow rates, and in reducing the likelihood of acute urinary retention and surgery. The follow-up period of the MTOPS trial was 4.5 years and another conclusion drawn from this study was that finasteride needs time to reveal its beneficial therapeutic capacity.

In another study examining combination therapy, it was shown that patients with lower urinary tract symptoms and moderately enlarged prostates initially receiving combination therapy with finasteride and an alpha-blocker were likely to experience no significant symptom deterioration after discontinuing the alpha-blocker following 9 to 12 months of combination therapy (34). A multicentre, placebo-controlled study (SMART study), [Symptom Management After Reducing Therapy], on the short term combination of dutasteride and tamsulosin involving 327 patients confirmed compatible results (35).

#### 4.2.1.4 CONCLUSIONS

- It has been shown in numerous randomized, placebo-controlled clinical trials that 5-alpha reductase inhibitors are capable of reducing prostate volume and improving symptom scores and flow rates. Maximum benefits are seen at a mean period after 6 months.
- Men with small prostates (< 40 mL) are less likely to benefit from finasteride.
- 5-alpha reductase inhibitors 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 10 years) effects of 5- alpha reductase inhibitors are substantial.
- The combination of a 5-alpha reductase inhibitor with an alpha-blocker seems beneficial according to the data currently available.
- Side-effects of 5-alpha reductase inhibitors are minimal
- Treatment with 5-alpha reductase inhibitors does not mask the detection of prostate carcinoma. By doubling PSA serum levels, an accurate estimation can be expected.

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#### 4.2.2 *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.

##### 4.2.2.1 *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, alpha1-adrenoceptors were identified and selective, better-tolerated, alpha-blockers were developed. A large number of alpha1-selective, alpha-blockers are available (tamsulosin, alfuzosin, doxazosin, indoramin, prazosin, terazosin). Broadly speaking, they all have a similar efficacy and side-effect profile.

#### 4.2.2.2 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 alpha1-receptors within the prostate and bladder neck. However, the exact contributions of alpha1-receptor subtypes and the 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.

#### 4.2.2.3 Pharmacokinetics

Alpha-blockers are taken orally and the dosage depends on the half-life of the relevant drug. Tamsulosin, alfuzosin, terazosin and doxazosin have the advantage of being long-acting, once-daily preparations.

#### 4.2.2.4 Assessment

It is not unreasonable to offer a trial of alpha-blockers to all men with uncomplicated LUTS. The optimal duration of the trial of therapy has been debated. Symptoms can improve within 48 hours. An I-PSS assessment requires at least one month of therapy. There is no justification in prolonging therapy beyond one month in men who do not respond. One-third of men will not experience significant symptom reduction. Currently there is no method of predicting which men will show a response (4).

#### 4.2.2.5 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. Because of this, secondary publications that have compared outcomes between these studies have been useful (5-7). Djavan and Marberger's meta-analysis estimated that overall symptoms improved by 30-40% and that flow rates improved by 16-25%, compared with placebo (6).

Predicting response for any individual is more difficult and therefore a trial of therapy is required. The various types of alpha-blockers cannot be distinguished by their ability to relieve symptoms or improve flow.

#### 4.2.2.6 Durability

Good data on long-term efficacy and the effect on natural history are currently not available. Long-term studies tend to be open-label extensions or increasingly 'real life practice' studies which do not conform to an experimental design. Nevertheless, in this context these types of design are informative.

Patients may choose to stop taking medication for a number of reasons. Studies have concentrated on two important reasons, namely, the occurrence of adverse effects and lack of efficacy (8). In general, the symptom status of men did not predict whether they were likely to stop therapy. Drop-outs occurred at the same rate, irrespective of whether symptoms were moderate or severe. The rate of drop-out in men on alpha-blockers appears to be between 0.01 and 1.6 per month. There is no evidence that efficacy diminishes with time.

#### 4.2.2.7 Adverse effects

The most commonly reported side-effects with alpha-blocker therapy are headaches, dizziness, postural hypotension, asthenia, drowsiness, nasal congestion and retrograde ejaculation (6). In general, the rate of side-effects in studies looking at tamsulosin and alfuzosin were equivalent to placebo (4-10%). Tamsulosin resulted in less orthostatic hypotension than alfuzosin under test conditions. Whether this translates into a reduction in clinical side-effects remains to be seen.

#### 4.2.2.8 Acute urinary retention

Early trials comparing alpha-blockers to placebo showed an increased likelihood of a successful trial, without catheter, following an episode of acute urinary retention. As a result, a large number of urologists have adopted this practice. The effect seems to be independent of the type of alpha-blocker studied. Two trials have looked at alfuzosin (11), and one at terazosin (12).

None of these trials continued therapy beyond the period of catheterization. Most men experience re-retention within the first two months (13). Studies are underway which address the question of whether men do benefit from alpha-blockade in the six months following acute urinary retention.

#### 4.2.2.9 CONCLUSIONS

- Alpha-blocker therapy can result in a rapid improvement in symptoms by a factor of 20-50% and an improvement in the 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 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.

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#### 4.2.3 Phytotherapeutic agents

The use of phytotherapy in treating lower urinary tract symptoms and benign prostatic hyperplasia has been popular in Europe for many years and has recently spread in the USA. These agents are composed of various plant extracts and it is always difficult to identify which component has the major biological activity. A few short term randomized trials and some meta-analyses show clinical efficacy without major side effects for compounds such as *Pygeum africanum* and *Serenoa repens* (1-4). In some studies the efficacy of these compounds was found to be equivalent to finasteride and  $\alpha$ -blockers (5,6). Many questions concerning the composition, the extraction and the mechanism of action of these compounds still remain unanswered and therefore additional randomized, placebo controlled trials are needed (7).

##### 4.2.3.1 CONCLUSIONS

The mode of action of phytotherapeutic agents is unknown. The biological effects are unclear although a few randomized clinical trials show encouraging results.

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### 4.3 Surgical management

Transurethral resection of the prostate (TURP), transurethral incision of the prostate (TUIP) and open prostatectomy are the conventional surgical options. Transurethral vaporisation, an electrosurgical modification of the TURP-technique, is also included to this chapter. Two randomized controlled trials (RCTs) are available

for open prostatectomy, while TURP, TUIP and TUVP have been subjected to a number of RCTs.

#### 4.3.1 *Indications for surgery*

The most frequent indication for surgical management is bothersome LUTS refractory to medical management (1,2). The following complications of BPH/BPE are considered strong indications for surgery:

- refractory urinary retention
- recurrent urinary retention
- recurrent haematuria refractory to medical treatment with 5-alpha reductase inhibitors
- renal insufficiency
- bladder stones.

Increased post-void residual volume may also be used as an indication for surgery. However, there is a great intra-individual variability and an upper limit requiring intervention has not been defined. Variables that most likely predict the outcome of prostatectomy are severity of LUTS, the degree of bother and the presence of BPO (see above) (3,4).

#### 4.3.2 *Choice of surgical treatment*

Ten RCT comparing TUIP to TURP are available (5-7). They showed similar improvements of LUTS in patients with small prostates (< 20-30 mL) and no middle lobe (5-7). TUIP has several advantages over TURP, such as a lower incidence of complications, minimal risk of bleeding and blood transfusion, decreased risk of retrograde ejaculation and shorter operating time and hospital stay, yet a higher long-term failure rate. TURP comprises 95% of all surgical procedures and is the treatment of choice for prostates sized 30-80mL. Intra- and postoperative complications are correlated with the size of the prostate and the length of the procedure. Open prostatectomy is the treatment of choice for large glands (> 80-100 mL), associated complications such as large bladder stones, or if resection of bladder diverticula is indicated (8-10). A recent RCT has shown that Holmium-laser enucleation leads to similar outcome as open prostatectomy for men with large glands (> 100 mL) at a significantly lower complication rate (11). TUVP is considered an alternative to TUIP and TURP, particularly for patients with bleeding disorders and small prostates.

Coagulating intermittent cutting, rotoresection and bipolar electrocautery are electrosurgical modifications of the conventional technique (12-14). Encouraging data are available for all these techniques, the data of large scale RCT are awaited with interest (12-14). As RCT-data are not yet available, these methods are not described in more detail below.

#### 4.3.3 *Perioperative antibiotics*

A known urinary tract infection should be treated before surgery (15,16). The routine use of prophylactic antibiotics remains controversial. However, antibiotics are recommended in patients on catheterisation prior to surgery.

#### 4.3.4 *Treatment outcome*

##### *LUTS*

All four surgical procedures (TURP, TUIP, TUVP and open prostatectomy) result in an improvement of LUTS exceeding 70%, with open prostatectomy leading to slightly superior results (4-11). Mean improvement of LUTS in a meta-analysis of 29 RCT with a TURP-arm was 71% (range: 66-76%) (6). In the 10 RCTs comparing TURP to TUIP, both procedures resulted in a similar improvement in symptoms after 12 months (5-7). The RCTs comparing TURP to TUVP also revealed similar improvements of LUTS in both study arms (6).

##### *Uroflowmetry*

The mean increase of Qmax following TURP is 115% (range: 80-150%) (6); in absolute terms + 9.7 mL/s (range: 4-11.6 mL/s) (6). Following TUVP, the Qmax increased by 155% (range: 128-182%) (6). The highest Qmax improvement (+175%) is seen after open prostatectomy (absolute numbers: 8.2-22.6 mL/s) (6,8-10).

##### *Post-void residual volume*

All four surgical procedures allow a reduction of the post-void residual volume of more than 50%: -65% after open prostatectomy; -60% after TUVP; -60% after TURP; and -55% after TUIP (4-11).

#### 4.3.5 *Complications*

##### *Intra-/peri-operative*

Mortality following prostatectomy has decreased significantly within the past two decades and is less than < 0.25% in contemporary series (6,17-19). The risk of a TUR-syndrome (fluid intoxication, serum Na<sup>+</sup> < 130 nmol/L) is in the range of 2%. Risk factors for the development of the TUR-syndrome are excessive bleeding with opening of venous sinuses, prolonged operation time, large glands and past or present smoking (20). The

estimated need for blood transfusion following TURP is in the range of 2-5%. Higher percentages have been reported following open prostatectomy (6,8-10). The risk of bleeding following TUIP and TUVP is negligible (6).

#### *Long-term complications*

**Incontinence:** Median probability for developing stress incontinence ranges is 1.8% following TUIP, 2.2% following TURP, and up to 10% following open prostatectomy (4-11). Limited information on this issue is available for TUVP; one RCT reported an incontinence rate of 5% (6,21).

**Bladder neck contracture and urethral stricture:** The risk of developing an urethral stricture is 2.6% after open prostatectomy, 3.8% after TURP and 1.7% after TUIP (4-11). The risk of bladder neck contracture is 1.8% after open surgery, 4% after TURP and 0,4% after TUIP (4-11). The respective figures for TUVP are in the range of TURP (6).

**Sexual function:** Retrograde ejaculation results from the destruction of the bladder neck and is reported in 80% after open prostatectomy, 65-70% after TURP and 40% after TUIP (4-11). There is a long-standing controversy on the impact of prostatectomy, particularly TURP, on erectile function. The only RCT that compared TURP to a “wait and see” policy reported identical rates of erectile dysfunction in both arms (4). In the 29 RCTs recently reviewed, the incidence of erectile dysfunction following TURP was 6.5% (95% CI: 0.2-12.7%) (6). The frequently reported rise of erectile dysfunction after TURP is therefore most likely not a direct consequence of TURP but rather caused by confounding factors, such as age.

#### 4.3.6 *Long-term outcome*

##### *Retreatment rate*

Favourable long-term outcome is common after open prostatectomy, TURP and TUIP. A secondary prostatic operation is reported at a constant rate of approximately 1-2% per year (4-11). Few data are available on the long-term outcome following TUVP.

##### *Long-term risk of mortality*

The possibility of an increased long-term risk of mortality after TURP compared to open surgery has been raised by Roos et al. (18). These findings have not been replicated by others (17,19,22).

#### **4.3.7 CONCLUSIONS AND RECOMMENDATIONS**

Surgery should be considered for those men:

- who are moderately/severely bothered by LUTS, yet who do not improve after non-surgical (including medical) treatment.
- with bothersome LUTS, who not want medical treatment but who request active intervention.
- with a strong indication for surgery.

In addition:

- Surgical prostatectomy (open, TURP, TUIP, TUVP) results in significant subjective and objective improvements superior to medical or minimally invasive treatment. All four surgical procedures have been evaluated in randomised controlled trials.
- TUIP is the surgical therapy of choice for men with prostates < 30 mL and no middle lobes.

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#### 4.4 Lasers

The use of lasers to treat BPH has been contemplated since 1986 but was anecdotal until the early 1990s (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.

##### 4.4.1 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).

##### 4.4.2 Right-angle fibres

From 1991 onward, 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 seconds) 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 of 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 and 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).

#### **4.4.3 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<sup>3</sup> 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.

#### *4.4.4 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- $\mu$ m 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. Gillig 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 versus 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).

#### 4.4.5 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)
- holmium laser prostatectomy is a viable alternative to TURP and irrespective of any anatomical configuration.

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

### 4.5.1 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.

### 4.5.2 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<sup>2</sup>. 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).

#### 4.5.3 *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. Haemospermia 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<sup>2</sup>. As a consequence, the maximum site intensity was set at 2.000 W/cm<sup>2</sup>.

#### 4.5.4 *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, Bihrlé et al. (7) reported on experience with 15 patients and a follow-up of 90 days. The Q<sub>max</sub> 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 Q<sub>max</sub> 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 Q<sub>max</sub> 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).

#### 4.5.5 *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% of patients 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 Q<sub>max</sub> and linear passive urethral resistance relation was 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.

#### 4.5.6 *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. Haemospermia 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.

#### 4.5.7 *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.

#### 4.5.8 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.

#### 4.5.9 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.

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## 4.6 TUNA®

### 4.6.1 Assessment

No specific diagnostic work-up prior to TUNA® is necessary.

### 4.6.2 Procedure

The TUNA® device delivers low-level, radio-frequency energy to the prostate via needles inserted transurethally (1).

### 4.6.3 Morbidity/complications

Is usually performed as an out-patient procedure under local anaesthesia, although intravenous sedation is required in some patients (1). 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 (1). Irritative voiding symptoms lasting up to 4-6 weeks are frequently present (2). Continence status is not affected.

### 4.6.4 Outcome

Several non-randomized clinical trials have documented the clinical efficacy of this procedure with a fairly consistent outcome (3-7). The symptomatic improvement reported ranged from 40-70%. These data are statistically significantly better than at baseline and surpass the expected placebo effect. Improvements in Qmax vary widely from 26-121% in non-retention patients. A recent report with 5 years follow up in 188 patients demonstrated a symptomatic improvement of 58% and an improvement in flow rate of 41%, 21.2% required additional treatment (8). There is no convincing evidence that prostate size is significantly reduced following TUNA® (7-9).

### 4.6.5 Randomized clinical trials

TUNA® has been compared with TURP in one trial (8) with 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®. Adverse events, such as bleeding, dysuria, erectile dysfunction, urinary tract infection or strictures, were more frequent in the TURP arm.

### 4.6.6 Impact on bladder outflow obstruction

The impact of TUNA® on bladder outflow obstruction as assessed by pressure-flow studies was determined in seven clinical studies (7-13). 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.

#### 4.6.7 Durability

Several authors have reported on the long-term efficacy of the TUNA<sup>®</sup> procedure. Within 1 year, positive results can be translated into percentages ranging from 5-42% (1). Schulman et al. (14) recently presented 3-year follow-up data on 49 patients after TUNA<sup>®</sup>. Improvement in Qmax exceeding 50% was seen in 53% of patients after 36 months. Ten patients (20%) underwent TURP because of an insufficient therapeutic response (1). Long-term follow-up data exceeding this time period are not yet available.

#### 4.6.8 Patient selection

Few selection criteria have been identified. TUNA<sup>®</sup> is not suitable for patients with prostate volumes exceeding 75 mL or isolated bladder neck obstruction.

#### 4.6.9 CONCLUSIONS

TUNA<sup>®</sup> 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 only one randomized controlled trial, and there is limited evidence of long-term efficacy.

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## 4.7 TUMT

### 4.7.1 Assessment

Diagnostic endoscopy is essential because it is important to identify the presence of an isolated enlarged middle lobe or an insufficient length of the prostatic urethra.

### 4.7.2 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: Prostatecare® (Brucker, France); ProstaLund® (Lund Systems, Sweden); and Targis® (Urologix, USA). On a conceptual basis, they are all similar in delivering microwave energy to the prostate with some type of feedback system. 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.

### 4.7.3 The microwave thermotherapy principle

Microwave thermotherapy devices 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. 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 in which they measure temperature.

### 4.7.4 Morbidity

Morbidity following TUMT is an important issue. Low-energy TUMT is well-tolerated by patients. 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 (2-6). In these cases, a catheter may be necessary for an average of 7 days.

High-energy treatment is also well-tolerated, although pain medication needs to be administered to most patients prior to or during therapy. 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%) (7,8). 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:** The standard operating software for the Prostatron® is version 2.0, and remarkably



similar clinical results have been reported worldwide from several centres (2-4,7,9-13). The clinical efficacy of TUMT has been confirmed in several randomized, SHAM-(placebo) controlled studies (4,5,14,15). 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 (16,17).

A randomized study comparing TUMT with TURP was performed by Dahlstrand et al. (3). 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%).

**High-energy protocol:** The first reports on the application of high-energy levels using ProstateSoft® 2.5 were published by de la Rosette et al. (18) and Devonec et al. (19) and demonstrated clinically significant improvements. More recently, the European BPH Study Group performed a multicentre study of 116 patients using high-energy TUMT (20). In this study, the mean Madsen score improved from 13.6 at baseline to 5.5 at 26 weeks. 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.

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 (21). 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 (22).

One-year follow-up results of a prospective randomized study comparing high-energy TUMT with TURP were reported recently (23). 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.

#### 4.7.5 High-intensity-dose protocol

Although the results following high-energy TUMT are good, changes to the ProstateSoft® software have recently been reported. It was concluded from clinical experience that a shorter duration of treatment did not alter efficacy or decrease morbidity (22). On a conceptual basis, the so-called ProstateSoft® 3.5 protocol differed significantly from former protocols. Firstly, the principle of stepwise energy increments was abandoned and the treatment was initiated at an 80 W energy level. Secondly, 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 ProstateSoft® 3.5 protocol can therefore be considered to be high-intensity-dose TUMT.

Pace et al. (24) found in 56 patients, at six months, a decrease in IPSS from 18.1 to 5.1, an increase in maximum flow from 9.1 mL/s to 17.8 mL/s and cavities within the prostatic tissue of 54 of the 56 patients (95%). De La Rosette et al. (26) found in 167 patients, at 12 months, a decrease in IPSS from 19.2 to 7.9 and an increase in maximum flow rate from 8.9 to 16.4.

#### 4.7.6 Prostatic temperature feedback treatment

A treatment protocol with calculated tissue necrosis based on simultaneous intraprostatic tissue temperature has been introduced with the ProstateLund Microwave apparatus (PLFT, ProstateLund Feedback Treatment) (27). In a prospective, randomized, international, multicentre study against TURP, there was no statistically significant differences between the 2 treatments in decrease in symptom score (66% vs 65%), quality of life (IPSS) (69% vs. 64%), increase in flow rate (74% vs. 94%) or decrease in detrusor pressure at max. flow rate (34% vs. 47%). Only decrease in prostate volume was higher in the TURP group (51%) than in the PLFT group (30%) (28).

#### 4.7.7 Durability

Several studies using low-energy thermotherapy report on surgical retreatment rates for up to 1 year of 11% (25) and 10% (20). On the other hand, Van Cauwelaert et al. (11) reported only low retreatment rates with significant subjective and objective improvements. Recently Tsai et al. (29) reported a 5-year retreatment rate in 45 patients of 84.4% with medication (46.7%) or endoscopic surgery (37.7%), while Daehlin et al. (30) found a retreatment rate after 5 years in 71 patients of 68%.

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. (5,18) additional TURP was performed in only three out of

116 patients. De Wildt et al. (31) confirmed these findings, documenting five surgical interventions at 1-year follow-up in 85 patients treated.

#### 4.7.8 Patient selection

As the morbidity is relatively low and the treatment can be performed without anaesthesia, patients in poor health are particularly good candidates for thermotherapy. In particular, such patients with retention can benefit from this treatment. Good results with regard to catheter release have been obtained, with a success rate of 72% after 6 months in 29 patients (32). In a larger study of 200 patients, with a follow up of 2 years in 155 patients, only 7% failed to respond (33).

#### 4.7.9 CONCLUSIONS

- High-energy 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.

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#### **4.8 RECOMMENDATIONS FOR TREATMENT**

1. The WW policy should be recommended to patients with mild symptoms that have minimal or no impact on their quality of life.
2. 5 ARI's are 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.
3. Alpha-blocker therapy is a treatment option for patients with bothersome LUTS who do not have an absolute indication for surgical treatment.
4. Surgical management (TURP, TUIP, open prostatectomy) is recommended as first-line treatment for patients with complications due to BPH with (an absolute indication for treatment of) LUTS.
5. Significant post-operative morbidity, disappointing long-term data and higher costs have resulted in a substantial decline in the clinical use of lasers. It is not recommended as a first-line surgical treatment for patients with LUTS, but may have a role in the treatment of high-risk patient subgroups.
6. HoLRP is a promising new technique with outcomes in the same range as those of TURP.
7. Transrectal HIFU therapy is currently not recommended as a therapeutic option for elderly men with LUTS and is considered an investigational therapy.
8. TUNA® is an encouraging technology as an alternative with acceptable results.
9. TUMT is an acceptable alternative to TURP and for those who prefer to avoid surgery or who no longer respond favourably to medication.

## **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**

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

*This list is not comprehensive for the most common abbreviations.*

AHCPR	Agency for Health Care Policy and Research
ALFIN study	European multicenter double-blind study to assess the efficacy and safety of Alfuzosin (5 mg twice daily) versus finasteride (5mg once daily) and the combination of both in patients with symptomatic BPH
ARI	alpha reductase inhibitor
AUA	American Urological Association
AUR	Acute urinary retention
BII	BPH Impact Index
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
DHT	dihydrotestosterone
DRE	digital rectal examination
EPCDS	European Prostate Cancer Detection Study
ERSPC	European Randomized Study of Screening for Prostate Cancer
HE-TUMT	high-energy thermotherapy
HIFU	high-intensity focused ultrasound
HoLRP	Holmium laser resection of the prostate
ICS	International Continence Society
I-PSS	International 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 study
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PPV	predictive positive value
PQSF	Prostate weight, Quality of life, Symptoms, Maximum flow rate
PSA	prostate-specific antigen
PVR	post-void residual volume
Qav	average flow
Qmax	maximum flow
Qm90	mean flow for middle 90% of voided volume
RCT	randomized controlled trial
ROC	Receiver Operating Characteristics
QoL	Quality of Life
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)

