Evaluation of
Minimally Invasive Surgical Techniques
in Clinical BPH

Objective and subjective results of

TURP, contact laser prostatectomy and electrovaporization

Harm van Melick

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Evaluation of Minimally Invasive Surgical Techniques in Clinical BPH

Objective and subjective results of TURP, contact laser prostatectomy and electrovaporization

Evaluatie van minimaal invasieve chirurgische technieken in klinische BPH

Objectieve en subjectieve resultaten van TURP, contact laser prostatectomie en electrovaporizatie

(met een samenvatting in het Nederlands)

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Wat vandaag algemeen bekend is,
Was gisteren wetenschap.

(Niels Bohr, fysicus)

Voor mijn moeder
Ter nagedachtenis aan mijn vader

CONTENTS

LIST OF ABBREVIATIONS

AG number	Abrams-Griffiths number
AUA	American Urological Association
BII	BPH Impact Index
BOO	Bladder Outlet Obstruction
BPE	Benign Prostatic Enlargement
BPH	Benign Prostatic Hyperplasia
BPO	Benign Prostatic Obstruction
BS	Bother Score (also: Symptom Problem index)
CE	Cost Effectiveness
CLP	Contact Laser Prostatectomy
DRE	Digital Rectal Examination
EVAP	Electrovaporization
HR	High-Risk
ILP	Interstitial Laser Prostatectomy
I-PSS	International Prostate Symptom Score
LUTS	Lower Urinary Tract Symptoms
NR	Normal-Risk
PSA	Prostate Specific Antigen
Qmax	Maximum urinary flow
QoL	Quality of Life
RCT	Randomized Controlled Trial
RF	Radio Frequency
SD	Standard Deviation
SPI	Symptom Problem Index (also: Bother Score)
TRUS	Transrectal Ultrasonography
TULIP	Transurethral Ultrasound-guided Laser-Induced Prostatectomy
TUMT	Transurethral Microwave Therapy
TUNA	Transurethral Needle Ablation of the Prostate
TURP	Transurethral Resection of the Prostate
URA	group-specific Urethral Resistance Algorithm
VLAP	Visual Laser Ablation of the Prostate
WHO	World Health Organization

CHAPTER 1

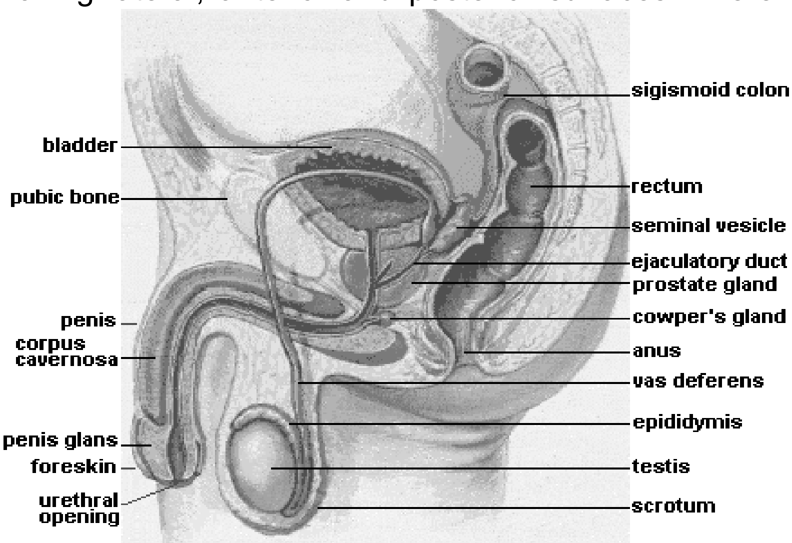
Introduction

The prostate is a small ovoid gland surrounding the proximal male urethra. Its function is the production of a part of the seminal fluid. By its natural history, some prostates will enlarge and by doing this, urinary outflow obstruction can occur. The process of benign enlarging is caused by hyperplasia. This gives the most common name for this pathological condition: Benign Prostatic Hyperplasia (BPH). Obstruction of urinary outflow might cause symptoms known as Lower Urinary Tract Symptoms (LUTS), although many other factors also can be involved. Treatment is possible in several ways depending on factors like severity of these symptoms, bothering caused by these symptoms and preference of patient and/ or physician.

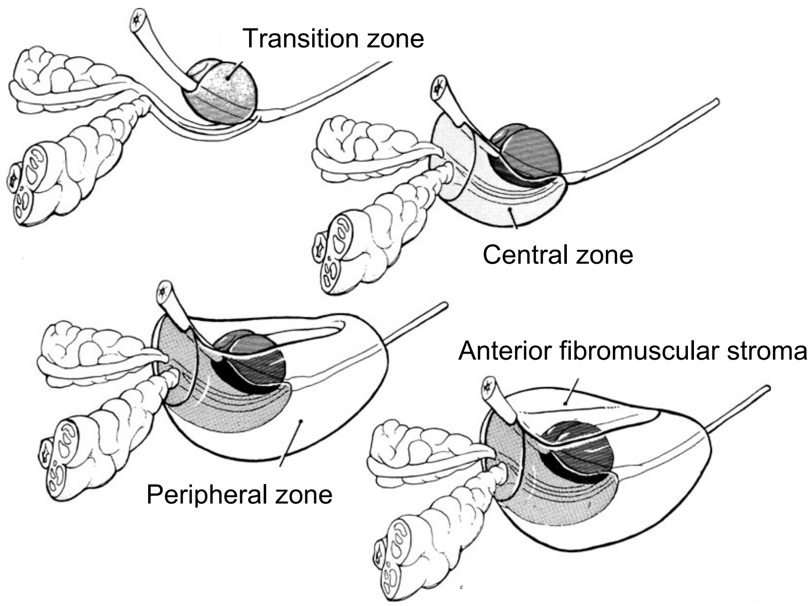
This thesis is focused on three different kinds of transurethral surgery. To explain the aims of this thesis, the context of benign prostatic hyperplasia will be described. The next paragraphs deal briefly with different anatomical and (patho)physiological aspects of the prostate, symptoms caused by BPH, diagnostic tests and different treatments.

1.1 ANATOMY AND PHYSIOLOGY

The prostate is a glandular, ovoid shaped organ based at the bottom of the bladder. It is present in all male mammals, although there is a considerable diversity in anatomy, biochemistry and pathology. In man, the prostate normally weighs about 20 g, has a length of 3 cm, is 4 cm wide and 2 cm deep. It is commonly referred to as having lateral, anterior and posterior surfaces. There is a narrowed apex inferiorly which is continuous with the striated urethral sphincter. Superiorly there is a broad basis bordering the base of the bladder. Some prostatic parts are adjacent to fascias of surrounding structures that form a sort of capsule. However, there is no true anatomic capsule[1].



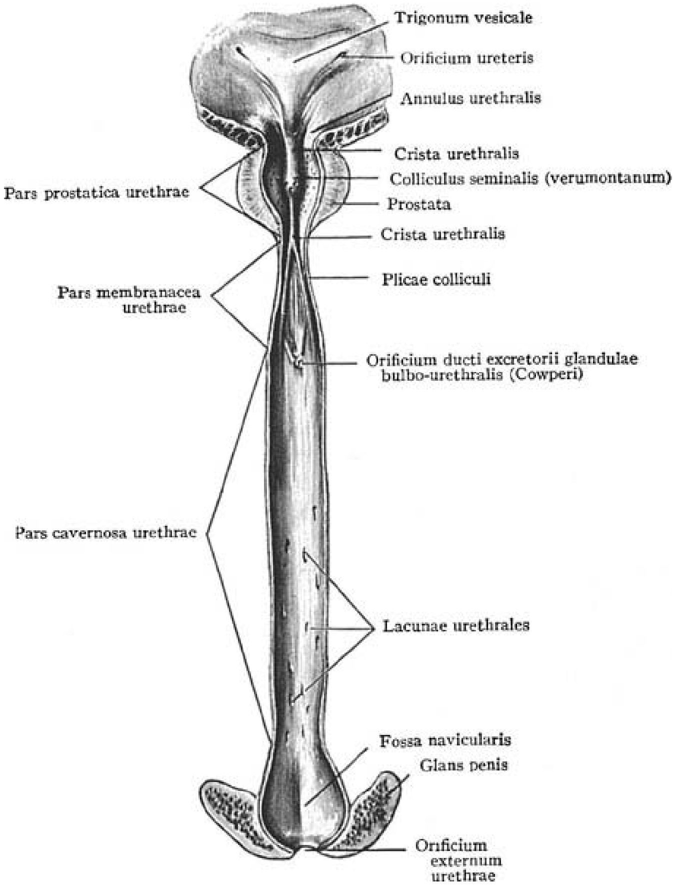
The prostate is composed of about 70% glandular tissue and 30% fibromuscular stroma. It can be divided into different zones: the central zone, the peripheral zone, the anterior fibromuscular stroma and the transition zone. The central zone is circumferentially to the ejaculatory ducts of the seminal vesicles at the posterior base of the prostate. It constitutes 25% of the prostatic glandular tissue. Hyperplasia or adenocarcinoma are rare in this zone (only 1 to 5% of all prostate cancers arise in this zone). The peripheral zone is the largest part with 70% of the glandular tissue. It is this part that accommodates 70% of the adenocarcinomas and is most affected by prostatic inflammation. Its posterior surface can be palpated by digital rectal examination. The anterior fibromuscular stroma can make up to 30% of the prostatic mass. Normally this part is nonglandular, but it can become glandular in adenomatous enlarged prostates. Finally, there is the transition zone that normally comprises only 5 to 10% of the glandular tissue. This zone is circumferentially to the urethra, which is named membranous or prostatic urethra in this region. The transition zone is the common region to become hyperplastic, causing benign prostatic hyperplasia (BPH). About 20% of the adenocarcinomas are thought to arise in this area. It is enclosed by a small fibromuscular band, that forms the surgical border when open prostatectomy is performed.



The prostate is made up of several components: epithelial, stromal, and non-cellular components. The tubuloalveolar glands of the prostate form acini, which are lined with epithelium. Some of these cells, luminal cells, produce specific products like prostate specific antigen (PSA): a secretory proteinase found in high concentration in semen. Only small plasma levels are found in healthy men, unless the barrier between these cells and blood vessels is damaged by inflammation or prostate cancer. Each acinus is surrounded by stroma containing fibroblasts and smooth muscle cells[2]. These stromal cells are amid a background of extracellular matrix made up of a divers group of glycoproteins. It forms a necessary framework in which all cells interact.

The urethral length, inside the prostatic transition zone, spans on average 2 to 2.5 cm (range: 1.2 to 5 cm)[3]. The proximal urethra is continuous with the smooth muscle of the bladder, which creates the preprostatic sphincter. This type of muscle pharmacologically differs from the rest of the bladder. It is stimulated by alpha-adrenergic fibers, which also stimulate the prostatic smooth muscles. This explains the pharmacodynamics of the very popular α-adrenoceptor antagonists, which are used in many men with bladder outlet obstruction. Continence can sometimes be maintained by the preprostatic sphincter in men with a destroyed striated urethral sphincter[4].

The urethra angulates halfway the prostate approximately 35 degrees anteriorly (range: 0 to 90 degrees). In the posterior midline, a crest projects into the urethra, which is named collicullus seminalis or verumontanum. It is an important landmark in transurethral surgery, that should be handled with care. At its apex, a small orifice is found, named the utriculus. It is a Müllerian remnant, also known as the 'male vagina'. In males with ambiguous genitalia, this structure can be well developed into a prostatic 'vagina'. Laterally of the utriculus are the two orifices of the ejaculatory ducts. These are connected with the seminal glands and the vasa deferentia. This is the place where semen, mixed with seminal fluid, enters the urethra and mixes with prostatic fluid. Laterally of the verumontanum grooves are formed, which are named prostatic sinuses.



All glandular elements of the prostate drain into these sinuses by several small orifices. This mixture of semen with different fluids forms the ejaculate, which is on average 3 ml. It is composed of high concentrations of many substances, of which the physiological function is at present only minimally known. They are probably not essential for fertilization, but they may optimize its conditions.

1.2 PATHOFYSIOLOGY, EPIDEMIOLOGY AND NATURAL HISTORY OF BPH

For unknown reasons, abnormal growth of the prostate is almost unique to human and dogs. It is not seen in other mammals. Also intriguing is the fact that this abnormal growth seems to be limited to the prostate. Embryologically related sex accessory tissues, like the seminal vesicles and bulbourethral glands, demonstrate only very rarely tumours. Many factors are involved in prostatic growth. The two long known etiologic factors for the development of BPH are aging and functional testes[5]. However, this concept is displaced by modern research which proposed a more complex concept of prostatic growth. Although this concept is unfinished, it involves many factors divided into intrinsic and extrinsic factors[6]. Intrinsic factors are derived directly from within the prostate: epithelial components, stromal components and the extracellular matrix interact with one another and provide a self-perpetuating growth mechanism using various growth factors. Extrinsic factors influence prostatic growth from external sources with the testes as most important organ. The testes form an endocrine organ that influences growth by several substances of which androgen is by far the most powerful mitogen. Other external factors are also important of which environmental and genetic factors are subject of scientific discussion.

If the balance between cell division and apoptosis leads to a numeric increase in cells, this is named hyperplasia. This can happen in the prostate leading to benign prostatic hyperplasia (BPH). The term hypertrophy, meaning increase in cellular volume, is pathologically incorrect. In the prostate, hyperplasia is almost exclusive for the periurethral transition zone[7]. Most seen is a form of nodular hyperplasia, in which both stromal and epithelial cells increase numerically. During the first 20 years of BPH development, there is an increase in the number of nodules[8], whereas in a later stage some of these nodules proliferate to become large nodes.

Autopsy studies revealed that BPH was not found in men younger than 30[5]. Prevalence of BPH increased after this age, peaking at 88% in men in their eighties[5]. This (microscopic) hyperplasia can lead to macroscopic BPH, also named benign prostatic enlargement (BPE). In about 50% of the men with microscopic BPH, this will lead to a macroscopically enlarged gland (BPE)[9,10,11].

Prostate size can be determined in several ways. In clinical practice, digital rectal examination (DRE) and transrectal ultrasound (TRUS) are commonly used. The volume of the normal prostate is about 20 ml by the third decade[5]. Cross-sectional studies have demonstrated a slow but ongoing increase in prostatic volume with age from approximately 25 ml for men in their fourth decade to about 35 to 45 ml for men in their eighth decade[12,13,14].

Benign prostatic enlargement (BPE) can lead to benign prostatic obstruction (BPO). This infravesical obstruction can compromise urinary flow and will induce changes in the bladder wall. Obstruction-induced changes lead to the development of detrusor smooth muscle hypertrophy, which is endoscopically seen as trabeculation.

1.3 LOWER URINARY TRACT SYMPTOMS (LUTS)

The relationship between the histologic (BPH), anatomical (BPE) and mechanical (BPO) entities on the one hand and urinary symptoms on the other hand is complex. The etiology of urinary symptoms has long been connected strongly to the prostate. In this way the term ‘prostatism’ was used for many male symptoms. It became clear however, that symptoms could be found in men with one, two, three or none of the aforementioned entities. Even in old males it is possible to find symptoms without prostatic pathology. Their symptoms can be caused by other age related pathology, like detrusor instability or low bladder volumes due to hypersensitivity or bladder carcinoma[15,16]. Other lower urinary tract pathology may also cause similar problems, like cystolithiasis, infection or prostate cancer[17,18]. The finding that similar urinary problems can also occur in women, provides further evidence that these symptoms can arise independent of prostatic presence[19,20,21].Therefore, the term lower urinary tract symptoms (LUTS) has been introduced[22]. It covers all voiding and storage symptoms, without stating anything about etiology or gender.

Table 1 showing a subdivision of lower urinary tract symptoms (LUTS).

Voiding symptoms	Storage symptoms
Weak urinary stream	Frequency
Abdominal straining	Nocturia
Hesitancy	Urgency
Intermittency	Incontinence
Incomplete bladder emptying	Bladder pain
Terminal en postmicturitional dribbling	
Dysuria	

Although voiding symptoms are very prevalent in men with LUTS associated with BPH, storage symptoms like urgency and nocturia appear to be the most bothersome[23].

LUTS can be quantified by using questionnaires developed by the American Urological Association (AUA). The measurement committee of the AUA developed the International Prostate Symptom Score (I-PSS) to quantify the prevalence of symptoms[24]. The I-PSS consists of seven questions, concerning incomplete emptying, frequency, intermittency, urgency, weak urinary stream, hesitancy and nocturia. Questions can be answered on a scale of 0 (not at all) to 5 (almost always). The sum of the scores forms the index, varying from 0 to 35, and is also known as the symptom score index. Of even more importance for treatment is the bothersomeness of these symptoms and their effect on the quality of life[25,26]. Therefore the AUA measurement committee also developed and validated a Symptom Problem Index (SPI) with 7 bothersomeness questions of which each corresponds to a symptom question of the I-PSS[27]. Each question can be answered on a scale of 0 (not at all) to 4 (very much), leading to an index varying from 0 to 28.

The same committee also developed a Quality of Life question:" If you were to spent the rest of your life with your urinary condition just the way it is now, how would you feel about that?". It can be scored from 0 (delighted) to 6 (terrible)[24]. Another AUA validated questionnaire, that quantifies how much urinary problems affect various domains of health, is the BPH Impact Index (BII)[27]. Most used is the I-PSS (ranging from 0 – 35), which is often utilized to classify patients according symptom severity: 0 to 7 points is classified as mildly symptomatic, 8 to 19 points as moderately symptomatic and those scoring 20 to 35 points as severely symptomatic. Worldwide epidemiologic studies demonstrated significant differences in symptom prevalence between nations, but an increase in symptoms with advancing age is always evident [28,29,30,31].

1.4 DIAGNOSTICS IN MEN PRESENTING WITH LUTS

The etiology of LUTS can vary and is certainly not always related to prostatic pathology. LUTS can be caused, or more generally, can be associated with (a combination of) BPE, BPH or BPO. BPE can be measured by DRE or TRUS. BPO can be measured by urodynamics. BPH can only be diagnosed microscopically and is not of interest in a clinical setting. As stated before, other lower urinary tract pathology may also cause LUTS.

The International Scientific Committee of the 5th International Consultation on BPH has made several recommendations in the diagnostic work-up of men presenting with LUTS[32]. Work-up is divided into an initial evaluation and a urologic (specialized) evaluation. Tests are divided into recommended and optional tests.

1.4.1 Initially recommended tests

History: an adequate medical history about (dis)functioning of the urinary tract in the context of the patient's general health is mandatory.

Quantification of symptoms: of major importance is the quantification of symptoms, their associated bothersomeness, their effect on quality of life and their impact on various domains of health. The AUA validated several questionnaires, which have been translated in many countries. These are described in the previous paragraph concerning LUTS.

Physical examination and digital rectal examination (DRE): DRE must inform the physician about size, consistency, tenderness, shape and irregularities suggestive for prostate cancer. Next to a DRE, a focused neurological examination together with examination of the external genital organs and the lower abdomen, should be performed.

Serum prostate specific antigen (PSA): measurement of PSA in combination with DRE increases the cancer detection rate. Although there is no causal relation between BPH and prostate cancer, age is an important risk factor in both diseases. Detection of cancer next to BPH can change therapeutic options.

Urinalysis: a simple test to determine if the patient has haematuria, proteinuria, pyuria or bacterial infection. It can provide information about different pathology which can cause LUTS, like urinary tract infection or bladder cancer.

Voiding diary: the use of a voiding diary or frequency-volume chart will inform the physician adequately about the number and volume of voids during daytime and nighttime. The use of one 24-hour frequency-volume chart is sufficient to gain insight into the voiding pattern of men with BPH[33].

1.4.2 Specialized, optional tests

Urinary flow rate estimation: urinary flow rate can be measured electronically throughout the course of micturition. It is a non-invasive urodynamic parameter. The maximum flow rate (Qmax) shows a strong correlation with BPO. Qmax is volume dependant[34] and voided volumes over 150 ml are necessary to estimate Qmax accurately[35]. A low Qmax does not differentiate between bladder outlet obstruction (BOO) or a weak detrusor muscle. A Qmax < 10 ml/s has only a positive predictive value of 70% for BOO[36].

Residual urine estimation: residual volume is the volume of urine that remains in the bladder directly after finishing micturition. In men without LUTS these volumes are less than 5 ml in 87% and less than 12 ml in 100%[37]. However, recently it was shown that 30% of elderly male volunteers without LUTS have residual volumes higher than 50 ml[38]. Residual volume can be measured exactly by postvoid catheterization or accurately determined by transabdominal ultrasound. Intra-individual variation is large[39,40].

Pressure-flow studies: these are a part of the urodynamic assessment. Urinary flow is recorded simultaneously with measurement of the bladder pressure. The latter is recorded invasively by a small catheter introduced transurethrally into the bladder. It is the only way to differentiate between a low maximum urinary flow (Qmax) secondary to bladder outlet obstruction (BOO) and patients with a low Qmax due to other pathology, like an impaired detrusor function or neurogenic bladder. This test is recommended if the initial evaluation, flow rate and postvoid residual urinary volume are not sufficient enough to make a diagnosis of BOO. Especially if surgery is one of the treatment options, pressure-flow studies can be valuable. The data that are generated by a pressure-flow study make it possible to categorize patients according to their urethral resistance, which results from the combination of flow and detrusor pressure. The introduction of a nomogram was in 1979[41], which categorized patients as obstructed, equivocal or unobstructed. There is still controversy about the demarcation of these different categories. Different methods have been developed to analyze and quantify pressure-flow plots[42]. In this thesis, the Schäfer's obstruction grade is mostly used. This classification system is derived from the linear passive urethral resistance relation (linPURR)[43]. The linPURR has to be plotted in a specific pressure-flow diagram, which is divided in seven areas corresponding to different outflow resistances. Patients with Schäfer grades 0 and 1 are called unobstructed, those with Schäfer grade 2 are similar to the previous mentioned equivocal men and those patients with Schäfer grades of 3 to 6 are called obstructed[44].

Filling cystometry: this test is not recommended in routine cases, but will be shortly mentioned here, because it is often used in the studies described in this thesis. It is part of a urodynamic evaluation in which the bladder is filled with saline through a transurethral or suprapubic catheter at a constant rate. Simultaneously bladder pressure is measured. Filling cystometry provides information about the maximum cystometric capacity, uncontrolled detrusor contractions and bladder compliance.

Transrectal ultrasonography (TRUS): TRUS provides the most accurate information about prostatic size[45]. DRE provides easily volume information, although the reliability across observers is poor[46] and is less precise than TRUS[47]. In BPH it is necessary to have adequate information about volume and shape because this can alter surgical options. Furthermore, if PSA and/ or DRE are suggestive for prostate cancer, TRUS can give additive information and can be used to guide a biopsy needle[17].

Imaging of the upper urinary tract: Imaging of kidneys, collecting system and ureters by intravenous urography (IVU) or ultrasound is not recommended. IVU's were performed almost routinely in the past, but only in a small proportion this lead to a change in management. Symptoms like haematuria or urolithiasis increase the likelihood of clinical relevant findings[48].

Endoscopy of the lower urinary tract: in earlier days, urethrocystoscopy was routinely performed in patients presenting with LUTS. However, the relation between the optical appearance of the prostatic region and treatment outcome is almost not studied and the general opinion is that this relationship is very poor. Visualization can be necessary to rule out other pathology. It should only be performed if symptoms like gross haematuria are presented or to select or rule out specific invasive treatments.

1.5 TREATMENT OF MEN WITH LUTS

Many options are available for today's men presenting with LUTS associated with benign prostatic pathology. Depending on bothersomeness of their symptoms and clinical parameters like prostatic volume and obstruction an optimal choice can be made in a shared process between physician and patient. Treatment options can be divided into: watchful waiting, medication, open surgery and transurethral (or minimally invasive) surgery and prostatic stenting. The different options will briefly be explained with emphasis on the minimally invasive treatment options.

1.5.1 Watchful waiting

A substantial amount of patients will present with LUTS, but will refuse or postpone medical or surgical therapy. Reasons can be that the symptoms are not bothersome enough, or that the potential complications or side-effects do not outweigh the inconvenience of their LUTS. Sometimes reassurance that there is no malignancy can be enough. In a Dutch study, 41% of patients referred to a urologist with LUTS, elected watchful waiting[49]. In a randomized study comparing watchful waiting to resection of the prostate in patients with moderate LUTS, a 3 year follow-up demonstrated treatment failure in 17% and 8.2% respectively[50].

1.5.2 Medication

Medical therapy can be divided into α_1-adrenoceptor antagonists (α-blockers), androgen suppression like 5α-reductase inhibitors and phytotherapeutics. Their introduction has significantly altered treatment strategies for men with LUTS and BPH. Prostatectomy was the only widely accepted treatment for these men before 1980. Medication does not achieve the subjective and objective improvements seen in prostatectomy, but there is still a clinical relevant change. Their advantage is that they have fewer and less severe side-effects and most of these effects are reversible[51].

α-blockers

The prostate and bladder neck contain smooth muscle cells with α-adrenoceptors which mediate tension[52]. This can cause a dynamic bladder outlet obstruction which explains its role in clinical BPH. Several α-adrenoceptor blockers have been developed, which can be classified according to their uroselectivity and serum elimination half-time. Multicenter, randomized, double-blind, placebo-controlled studies have demonstrated safety, efficacy and durability of long-acting α-blockers like alfuzosin and tamsulosin. Symptom reduction is in the range of 1-4 I-PSS points and maximum flow increase is about 1-4 ml/s[53,54,55], which is significantly better than with placebo in most studies. Only a few urodynamic studies have been conducted, demonstrating some small, but significant, changes in urodynamic parameters[56].

androgen suppression

The embryonic development, and in later life, the development of BPH, are androgen dependant processes. The most abundant circulating androgen is testosterone, secreted primarily by the testes. This is partially converted to dihydrotestosterone (DHT), by the enzyme 5-α reductase. DHT is about twice as potent as testosterone in the prostate and it also has a greater affinity for its prostate receptor[57,58]. Surgical castration leads to a volume decrease of about 30%[59,60]. Most used is the selective type 2, 5-α reductase inhibitor finasteride. It reduces prostatic volume with 19-23%[61,62,63,64,63,64]. However, prostatic volume is only of minor importance in the pathophysiology of clinical BPH. The longest-duration study with finasteride is the Proscar Long-term Efficacy Study (PLESS)[65]. Baseline prostatic volume was about 55 ml. After 4 years, symptom score index decreased with 2.0 points, maximum flow rate increased with 1.7 ml/s and prostate volume reduced with 32%. Treatment with finasteride for up to 2 years halves the frequency of acute urinary retention and reduces the need for prostatic surgery by 55% compared to placebo in patients with moderate LUTS[66]. It is well tolerated and has a good safety profile[67]. Efficacy has only been proven in prostates sized over 40 ml[68]. Finasteride reduces the group mean serum PSA by about 50%[69], although the individual effect is highly variable.

phytotherapeutics

Phytotherapeutics, or plant extracts, are complex mixtures of different ingredients. Their use varies per country, with market shares of up to 50% in Germany and France[70]. Large patient numbers have sometimes already used some of these therapeutics before they see a physician for LUTS[71]. Their mechanisms of action are often unknown. Some suggested modes of action are: anti-androgenic, anti-estrogenic, inhibition of 5-α reductase or anti-inflammatory[72]. Clinical studies have been conducted with extracts from, for example, Serenoa Repens (Saw palmetta) and Pygeum africanum (African plum tree). Several meta-analyses have been published about Saw palmetto that support some positive effects on LUTS. One of these, published by Wilt et al.[73] calculated mean weighted differences compared to placebo: these were a 1.41 point improvement in symptom score, an increase in maximum urinary flow of 1.93 ml/s and a reduction in nocturia of 0.76 per night.

1.5.3 Open prostatectomy

This procedure was one of the first surgical interventions in urology. It can be performed suprapubically, as was first done in 1894 and popularized by Freyer[74,75], or retropubically, as was popularized by Millin[76]. A complete resection of the hyperplastic adenoma can be achieved, with a maximum relieve in obstruction. The procedure was unchallenged, until TURP became popular in the sixties of the last century. There are almost no randomized trials comparing open prostatectomy to TURP[77]. Most important differences are an abdominal incision and longer hospitalization. An open procedure is advantageous over TURP in prostates sized over 80-100 ml and in patients with coexisting pathology that needs surgery.

1.5.4 Transurethral (or minimally invasive) prostatectomy

In the first half of the last century, open prostatectomy was by far the most performed surgical procedure for clinical BPH. It was not until the 1960s that new developments improved the quality of endoscopic surgery. In this way transurethral resection of the prostate (TURP) became the most popular surgical modality. Unfortunately, its success caused a historical, scientific gap, that will never be filled. One did not wait for a decent evaluation of the outcome of this kind of surgery. Besides one small randomized study, there has been no comparison between open prostatectomy and TURP[77]. Nowadays, it is considered unethical to perform a randomized trial comparing these two techniques[78]. TURP became the gold standard, and it is still considered to be so at this moment. However, TURP is associated with a significant mortality and morbidity, especially bleeding and perforation. This can make re-operation or transfusion necessary. In reaction to these findings, modern technologies were used to develop new modalities that were less invasive. They wanted to match the results of TURP, but with less side-effects, short hospitalization and, preferably, lower costs.

This led to the development of a variety of new minimally invasive treatment modalities, mostly using heat to remove excess of prostatic tissue. Methods of applying heat varied from radio frequency waves, and electric currents, to laser beams.

The heat applied to the prostate, causes tissue effects depending on temperature and duration of the heating process. The different effects will shortly be discussed, categorized by increasing temperatures:

40°C - 45°C: increasing temperature slightly over body temperature is called 'hyperthermia'. This process is used in malignant processes, where it causes permanent damage, because malignant cells are more sensitive to heat than normal cells.
45°C - 60°C: when heat is applied for more than ten seconds, this temperature causes irreversible protein denaturation.
60°C - 100°C: irreversible damage by protein denaturation is caused within tenths of a second.
100°C: at this temperature water starts to boil and all excessive heat is used for vaporization. Inside the cellular membrane, pressure will increase as vaporization starts until the membrane burst. This phenomenon causes an audible effect, named 'popcorn' effect[79].
Higher than 100°C: when tissue water has vaporized, all extra heat will increase temperature rapidly. The remaining dehydrated structures will caramelize and carbonize, creating a dark brown and black appearance, respectively.

The modalities that are still used in a clinical or scientific setting will be described below, with extra attention to the three modalities that are studied in this thesis: TURP, contact laser and electrovaporization.

Transurethral Resection of the Prostate: TURP

Transurethral resection of the prostate (TURP) was introduced in the United States in the 1920s and 1930s. Small lenses were placed in a rigid tube, to gain urethral access. In 1932, a system was built that made it possible to resect tissue electrically under direct visualization. The development of fiberoptic lighting in the 1970s in combination with wide-angle optic systems, caused a major improvement in endoscopical visualisation[80,81,82]. TURP overtook the leading position of the open prostatectomy and became the gold standard for surgical management of BPH.
TURP is performed by a transurethrally introduced resectoscope, with a semicircular wire, the resection loop, at the end. This loops forms the active electrode and electricity flows from this electrode into the surrounding tissue and back to the passive, return electrode. The latter is a large surface patch, placed on the patient's thigh or back. An insulation fluid, like isotonic glycine, surrounds the resection loop to prevent tissues that are not in direct contact with the electrode. Demineralized water would work perfectly, but water causes hemolysis[83]. The current density around the small surface of the active electrode is very high causing a direct cutting effect with only minimal tissue changes in the surrounding. Even cells at a few millimeters are not coagulated[84,85]. In this way prostatic chips can be removed, but large vessels may cause bleeding. A round, coagulation electrode with a larger surface area is than needed. Current density is lower and this causes a more gradual increase in

temperature that diffuses to a larger volume[86]. Most used is the technique described by Nesbit half a century ago[80], in which the resection is performed in a routine, step-by-step manner. Prostatic chips can be sent for histological examination. In men with at least one prior prostate biopsy, prostate cancer was found in 16.1%, although routine exclusion by PSA, DRE and TRUS had been performed before the time of surgery[87].
TURP is associated with a mortality form 0% to 0.8% within 1 month Postoperatively and 2.8% within one year[88,89,90,91]. Intra-operative morbidity varies from 6.9% to 14%[90,91], especially bleeding and perforation. Morbidity within 30 days Postoperatively varies from 9.5% to 18%[90,91] and consists mainly of bleeding with or without clot retention. This can make re-operation or transfusion necessary. Late morbidity mainly consists of urethral strictures and bladder neck contractures and is reported in up to 11.2% within 12 months[88]. Transurethral resection syndrome occurs in about 2%[89]. It is caused by dilution effects of absorbed irrigation fluid. It is characterized by mental confusion, nausea, vomiting, hypertension, bradycardia and visual disturbance.

Electrovaporization

The electrosurgical properties depend highly on the shape and surface area of the active electrode. The small wire in the TURP electrode leads to tissue dissection and the roller ball leads to coagulation. A further development of a large surface area lead to the construction of electrovaporizators. They are often constructed as a grooved roller bar, like the Vaportrode (Circon-ACMI, Stamford, Conn, USA). The active element consists of a grooved cylinder that is 3 mm wide and 3 mm in diameter, that can move around a small horizontal axis. Prostatic tissue coagulates and vaporizes in contact with the grooves. Similar to TURP, glycine is used as an irrigation fluid. There are no prostatic chips that can be sent for pathological examination, as all tissue is vaporized. An important difference between TURP and electrovaporization in the use of the electrosurgical generator. In TURP, there is always a fresh native layer of prostatic tissue left behind after resection that causes only small changes in impedance. Electrovaporization however, causes a few millimeters thick coagulated layer, which increases electrical impedance. To optimize performance, it is necessary to use an impedance independent generator that delivers sufficient power[92]. Recently, newly shaped electrovaporizators have been introduced that combine the shape of the standard TURP loop together with a grooved roller bar into a ‘vaporizing loop’, which resects and vaporizes at the same time.

Transurethral Needle Ablation: TUNA

TUNA uses low-level radio frequency (RF) energy to generate heat. This technique had previously been used in cardiology to destroy the additional nervous pathway in the Wolff-Parkinson-White syndrome[93] and to destroy malignancies[94]. The TUNA generator (Vidamed, Menlo Park, California, USA) produces a monopolar RF signal of 490 kHz. This signal is transduced along a special transurethral instrument and two special antennas at the end of the tip, into the prostatic tissue. A patch is adhered to the patient's skin that serves as a return electrode. It generates a tissue heating varying from 80-100°C, enough to create 1-cm necrotic lesions[95]. TUNA can be used with topical anaesthesia. Clinical results are close to TURP, although long-term results are limited[96]. The most common complication is post-operative urinary retention in up to 40% of patients[97].

Transurethral Microwave Therapy: TUMT

Similar to TUNA, radio frequency energy is used to heat tissue, but in TUMT the frequency is much higher. Depending on the type of generator used, RF's vary from 902, to 1296 or 1928 MHz. These RF's penetrate tissue deeper than those generated by TUNA. TUMT can therefore heat a larger area, but with a lower temperature[98]. This modality was introduced as a transrectal instrument, generating temperatures of 42 - 44°C with limited clinical results[99,100]. A transurethral device was developed, which could increase prostatic temperatures to 70°C. Since its introduction there has been an evolution in this technique in which the applied energy increased from low-energy TUMT to high-energy TUMT. There are different theories explaining the clinical results. Histological studies demonstrated cellular apoptosis and necrosis[101,102]. Another controlled, histological study demonstrated statistical significant difference in prostatic α-adrenocepter density[103]. This would suggest a working mechanism, based on the assumption that there is a dynamic component in prostatic obstruction. The α-adrenoceptor antagonists intervene in a different way at this component. Clinical studies demonstrate good (long-term) symptomatic results with a lower morbidity than TURP[104,105,106,107].

Laser therapy

The term laser is an acronym describing its mechanism[108]. It stands for **l**ight **a**mplification by **s**timulated **e**mission of **r**adiation. A laser has several specifications that make it very interesting for specialized purposes: it produces monochromatic light, in a coherent, narrow collimated beam and a high energy density can be obtained. In this way it can be transported through small optical fibers (100 – 1000 μm) and used for specific tissues. There are different types of laser, depending on the medium used to emit light. Four types are used to treat the prostate:

Neodymium: Yttrium-Aluminium-Garnet (Nd:YAG) Laser: This laser consists of a YAG rod with the addition of neodymium atoms. It emits near infrared light at a wavelength of 1064 nm in a continuous wave. This light is poorly absorbed by water and body pigments, which causes it to penetrate relatively deeply. It has good coagulative characteristics.
Potassium Titanyl Phosphate (KTP) Laser: This type of laser uses a KTP crystal to double the frequency of a Nd:YAG laser, creating a wavelength of 532 nm. Tissue penetration is only half, but energy density is doubled, which increases its vaporization and desiccation characteristics.
Holmium: Yttrium-Aluminium-Garnet (Ho:YAG) Laser: A YAG rod mixed with holmium atoms creates a wavelength of 2100 nm, that is emitted in a series of rapid pulses over a few milliseconds. It produces a cutting effect by vaporization of tissue water and has low haemostatic properties.
Diode Laser: this a small laser emitting light of 800 – 1000 nm. It does not require large cooling devices, necessary for the aforementioned laser types.

The energy of these different lasers is mostly delivered transurethrally by an optical fiber. There are however, important differences in the last part of the route where laser energy is transferred to the prostatic tissue. There are three different delivering procedures:

End firing fibers: laser light is emitted at the end of the fiber and is either directly beamed at the prostate (bare tip) or the light heats a tip which is distally connected to the fiber, e.g. the sapphire tipped contact laser.
Side firing fibers: also named visual laser ablation of the prostate (VLAP). These fibers incorporate distally a prismatic internal reflector or they have an external glass or metal reflector. Laser light is mostly deflected at an angle of 90 degrees.
Interstitial fibers: these fibers are introduced directly into the prostatic tissue at different sides.

Most research has been conducted with Nd:YAG lasers with contact probes (contact laser prostatectomy: CLP), or side fire devices (visual laser ablation of the prostate: VLAP) or interstitial laser devices (interstitial laser prostatectomy: ILP). Unlike TURP, but similar to most other new treatment modalities, there is no tissue available for histology. Prostatic biopsy should be performed if there is any suspicion of prostate cancer.

Visual Laser Ablation of the Prostate: VLAP

This side firing laser device uses Nd:YAG generated laser light. It was one of the first laser techniques used in the treatment of BPH and is probably the most studied type in laser prostatectomy. One of the earliest systems used, was transurethral ultrasound-guided laser-induced prostatectomy (TULIP), which used an ultrasonic transducer. The entire prostate could be treated in this way. Although some success, this complex device did not stand the test of time[109]. In all other systems, surgery is performed under direct visualization of the laser tip and prostatic tissue. The most used method in VLAP is that of coagulation necrosis. Laser light is deflected towards the prostatic tissue for 30 – 60 seconds at different clock positions in the prostate. The depth of tissue destruction varies depending on tissue properties and laser settings and is typically 10 – 12 mm[110]. Temperatures of 70 – 90°C are reached. This results in a slow tissue sloughing taking several weeks, making catheterization necessary. Initial results were reported by Costello in 1992[111]. Later, studies randomized VLAP to TURP and demonstrated that VLAP resulted in subjective and objective improvements close to TURP[112,113]. Blood loss is minimal[112,114] and it can be performed on patients using anticoagulant or with bleeding disorders[115,116].

Interstitial Laser Prostatectomy: ILP

Interstitial laser prostatectomy was developed to address the problem of slow tissue sloughing that happens in VLAP. A small fiber is transurethrally (sometimes perineally) introduced into the prostate. A Nd:YAG or, more recently, a diode laser generates laser light to induce prostatic coagulative necrosis. In this way the integrity of the prostatic urethra can be preserved. There is no tissue sloughing, because all necrosis is removed by the process of tissue repair. The first publication was in 1993 by McNicholas[117]. Nd:YAG ILP has demonstrated to result in significant improvements, both symptomatically and urodynamically[118]. ILP has been used in patients while continuing warfarin anticoagulant therapy with fair results[119].

Contact Laser Prostatectomy: CLP

This modality uses laser light in a very different way than VLAP or ILP. In the two latter methods, laser light induces a thermal coagulative necrosis. In this way there is no direct removing of tissue like in TURP. CLP is often, but not necessarily, used in combination with a Nd:YAG laser. Laser light heats a synthetic sapphire tip attached to the distal end of the optical fiber[120]. This tip is provided with a black infrared-absorbent coating. Laser energy is than converted to thermal energy which increases temperature to several hundred degrees Celsius. In direct contact with prostatic tissue this causes a thermal induced vaporization which directly creates a cavity like in TURP. The effect is limited to a maximum penetration of about 1 mm, as apposed to the side-fire technique, in which the laser energy may penetrate as far as 1 cm into tissue. As opposed to the native layer of prostatic tissue that is left behind by TURP, there is a coagulated surface after CLP that minimizes bleeding. Some studies described the use of CLP in patients using anticoagulants with fair results[121,122]. Saline is used as irrigant, protecting for the TUR syndrome. Most tissue is removed (vaporized) immediately, so there is minimal tissue sloughing postoperatively.

1.5.5 Stents

A completely different approach is the use of a small intraprostatic stent. Stents were first introduced by Dotter in 1969[123] to stent peripheral blood vessels. In 1980, the first description of the use of stents in the obstructing prostate is presented[124]. Stents can be divided into permanent and temporary stents. Permanent stents were first introduced as a definite solution for obstructive prostates, often in studies with patients unfit for surgery. Complications were high and there are almost no publications in recent literature about the use of permanent stents as treatment for BPH[125,126,127]. Temporary stents receive more recent attention[128]. They are either made of nonabsorbable or biodegradable materials, of which the former need to be replaced every 6 to 36 months, depending on type and tissue properties. Biodegradable and some modern nonabsorbable stents with shape memory properties, are nowadays often used in combination with other minimally invasive treatment modalities that cause secondary or temporary obstruction, like side-fire laser prostatectomy and transurethral microwave therapy[129,130]. In this way, patients are not bothered by the use of a transurethral catheter.

1.6 AIMS OF THIS THESIS

Urodynamics is the only way to quantify bladder outlet obstruction, detrusor contractility and lower urinary tract parameters like detrusor instabilities, bladder compliance and cystometric capacity. It is recommended by the International Scientific Committee of the 5th International Consultation on BPH, if the initial evaluation, flow rate and postvoid residual urinary volume are not sufficient enough to make a diagnosis of BOO. Especially if surgery is one of the treatment options, pressure-flow studies can be valuable. Scientifically, it provides objective information about (dis)functioning of the lower urinary tract as opposed to quantified subjective information by AUA validated questionnaires. Urodynamics make it possible to categorize patients according to their outflow resistance. In this way patients can be classified as obstructed, equivocal or unobstructed. However, the demarcation of the borders between these categories is somehow arbitrarily.

It is generally accepted that men with high urethral resistance preoperatively benefit most from bladder outlet obstruction relief. Therefore physicians are rather reserved about resection of the prostate in equivocal and unobstructed men. A problem arises when a man with considerable LUTS and benign prostatic enlargement (BPE), but without infravesical obstruction or other pathology does not want medication at all, does not benefit from medication or does not tolerate this treatment.

This problem created the first aim of this thesis:

To evaluate the results of TURP in men with LUTS and BPH who are urodynamically not obstructed or equivocal and to compare these results with those in men who are urodynamically obstructed.

Many new minimally invasive surgical modalities have been introduced in the last decade to challenge the gold standard TURP. Contact laser prostatectomy and electrovaporization are two of these modalities. Modern scientific standards require a methodologically solid comparison of new techniques with the gold standard TURP.

This led to the second aim of this thesis:

To evaluate the results of TURP, contact laser prostatectomy and electrovaporization of the prostate.

During the initial use of laser prostatectomy it became obvious that the amount of blood loss is minimal. This characteristic makes it interesting to apply laser prostatectomy in a population of men with LUTS associated with BPH who are contraindicated for TURP, because they use anticoagulants or suffer from bleeding disorders.

This led to the third aim:

To evaluate the results of laser prostatectomy in men with LUTS associated with BPH who use anticoagulants or suffer from bleeding disorders.

1.7 OUTLINES OF THIS THESIS

Chapters 2 and 3 deal with the first aim of this thesis.

In **chapter 2** men presenting with LUTS associated with BPH are preoperatively and 6 months postoperatively urodynamically analyzed using uroflowmetry, filling cystometry and pressure-flow analysis. At the same time intervals they complete I-PSS, SPI, QoL question and BII. Patients are treated with the gold standard, TURP. In this way, the relation between objective urodynamic parameters on the one hand and quantified symptomatic and subjective changes on the other hand are determined. These correlations are used to predict outcomes of TURP according to preoperative urodynamic values.

In **chapter 3** a selected group of men with considerable LUTS and BPE opted for surgery, although urodynamics showed an equivocal or unobstructed urinary outflow. These men are treated with TURP. A second group of men who are urodynamically obstructed also undergoes TURP. Urodynamics are performed preoperatively and 6 months postoperatively. Symptoms, bother, quality of life and impact on general health are quantified using the appropriate AUA questionnaires. The quantified improvement six months after transurethral prostatectomy in the unobstructed and equivocal men are compared to the outcomes of transurethral prostatectomy in the obstructed men.

Chapters 4 to 7 deal with the second aim of this thesis.

A prospective randomized controlled study was carried out between 1996 and 2001 at our clinic to compare the three different treatment modalities. The results of this trial are presented in chapters 4 to 7. Included were men over 45 years of age with LUTS associated with BPH. All patients underwent history taking, digital rectal examination, transrectal ultrasonography, urodynamic evaluation, free flowmetry, post-void residual volume estimation, urinalysis and blood analysis.
Patients had to be urodynamically equivocal or obstructed (Schäfer obstruction grade $\geq$2). Their prostate volume had to be between 20 and 65 ml. Patients with any of the exclusion criteria of the International Consensus Committee on BPH were excluded from analysis. Group sizes were calculated with a power of 90% and statistical significance was set at 5%.

In **chapter 4** TURP, contact laser prostatectomy (CLP) and electrovaporization, are compared urodynamically. Pressure-flow studies, filling cystometry and uroflowmetry are performed preoperatively and 6 months postoperatively.

In **chapter 5** the three modalities are compared using the AUA validated questionnaires. Subjective changes are quantified using the International Prostate Symptom Scores (I-PSS), Symptom Problem Index (SPI), Quality of Life (QoL) question and BPH Impact Index (BII). Preoperatively and the first six weeks postoperatively these indexes are measured weekly and later at 3, 6 and 12 months. Next to objective complications, some specific morbidity and symptomatic aspects are studied using a self-developed questionnaire that is completed by all patients. The questionnaire is completed once preoperatively. Postoperatively it is filled out at a weekly interval during the first six weeks and later at 3, 6 and 12 months. Questions concern pain in the lower abdomino-genital region, pain during voiding, haematuria, incontinence, urge and hesitation. Together with the morbidity questionnaire, patients are asked to report the average number of voids during the daytime and nighttime for the last week.

In **chapter 6** the long-term results are studied. In fall 2002, all patients who were operated on for more than 18 months ago are re-invited to visit the outpatient department. Patients who were previously excluded, are not invited. In this way, follow-up times vary individually from 1.5 to 7 years. The same questionnaires are used as during the 12 months follow-up: I-PSS, SPI, QoL question, BII, the morbidity questionnaires and frequency during daytime and nighttime. Uroflowmetry is performed at the outpatient department.

In **chapter 7** some economic aspects of the different surgical approaches are regarded. Resources are limited and there is an increase in patients presenting with LUTS together with an increase in treatment modalities. Therefore, choices between (surgical) treatment modalities should also be based on economic aspects. The International Consultation on BPH recommends to perform a economic analysis for all new developed technologies. Until now these have not been performed for electrovaporization and CLP.

Chapter 8 deals with the third aim of this thesis.

In **chapter 8** a study is presented that describes the use of CLP and a combination of CLP with VLAP in so called high-risk patients. These are defined as patients using anticoagulants (acenocoumarol or fenprocoumon), using platelet aggregation inhibitors or suffering from various bleeding disorders. The patients which are treated with CLP in our randomized controlled trial are used as a reference group (normal risk patients). All patients are analyzed preoperatively and 6 months postoperatively using the aforementioned AUA validated questionnaires and urodynamics, including uroflowmetry, filling cystometry and pressure-flow analysis.

In **chapter 9**, finally, this thesis is generally discussed, final conclusions are made and futute perspectives are described.

Chapter 10 comprises a summary in Dutch.

References

1. Epstein J. I.: The prostate and seminal vesicles. In: Diagnostic surgical pathology. Edited by Sternberg, S.S. First edition, Raven press, New York, USA, pp.1393-1432, 1989.

2. Nemeth, J.A. and Lee, C.: Prostatic ductal system in rats: regional variation in stromal organization. Prostate, 28: 124-128, 1996.

3. Myers, R.P.: Male urethral sphincteric anatomy and radical prostatectomy. Urol. Clin. North Am., 18: 211-227, 1991.

4. Waterhouse, K., Abrahams, J.I., Gruber, H., Hackett, R.E., Patil, U.B., and Peng, B.K.: The transpubic approach to the lower urinary tract. J. Urol., 109: 486-490, 1973.

5. Berry, S.J., Coffey, D.S., Walsh, P.C., and Ewing, L.L.: Development of human benign prostatic hyperplasia with age. J. Urol., 132: 474- 1984.

6. Lee, C., Kozlowski, J.M., and Grayhack, J.T.: Intrinsic and extrinsic factors controlling benign prostatic growth. Prostate, 31: 131-138, 1997.

7. McNeal, J.E.: Origin and evolution of benign prostatic enlargement. Invest. Urol., 15: 340-345, 1978.

8. McNeal, J.: Pathology of benign prostatic hyperplasia. Insight into etiology. Urol. Clin. North Am., 17: 477-486, 1990.

9. Jacobsen, S.J., Girman, C.J., Guess, H.A., Rhodes, T., Oesterling, J.E., and Lieber, M.M.: Natural history of prostatism: longitudinal changes in voiding symptoms in community dwelling men. J. Urol., 155: 595-600, 1996.

10. Arrighi, H.M., Metter, E.J., Guess, H.A., and Fozzard, J.L.: Natural history of benign prostatic hyperplasia and risk of prostatectomy. The Baltimore Longitudinal Study of Aging. Urol., 38: 4-8, 1991.

11. Guess, H.A., Arrighi, H.M., Metter, E.J., and Fozard, J.L.: Cumulative prevalence of prostatism matches the autopsy prevalence of benign prostatic hyperplasia. Prostate, 17: 241-246, 1990.

12. Overland, G.B., Vatten, L., Rhodes, T., DeMuro, C., Jacobsen, G., Vada, K., Angelsen, A., and Girman, C. J.: Lower urinary tract symptoms, prostate volume and uroflow in norwegian community men. Eur. Urol., 39: 36-41, 2001.

13. Oesterling, J.E., Jacobsen, S.J., Chute, C.G., Guess, H.A., Girman, C.J., Panser, L.A., and Lieber, M.M.: Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA, 270: 860-864, 1993.

14. Jakobsen, H., Torp-Pedersen, S., and Juul, N.: Ultrasonic evaluation of age-related human prostatic growth and development of benign prostatic hyperplasia. Scand. J. Urol. Nephrol. Suppl, 107: 26-31, 1988.

15. Jepsen, J.V. and Bruskewitz, R.C.: Office evaluation of men with lower urinary tract symptoms. Urol. Clin. North Am., 25: 545-554, 1998.

16. Abrams, P.: Winds of change; BPH, BPE, BPO, or BOO? Be specific! Urol. Int., 10-11, 1996.

17. Kirby, R.S. and McConnell, J.: Benign Prostatic Hyperplasia. In: Fast Facts. Second edition, Health press limited, Oxford: pp. 64, 1999.

18. DuBeau, C.E. and Resnick, N.M.: Controversies in the diagnosis and management of benign prostatic hypertrophy. Adv. Intern. Med., 37: 55-83, 1992.

19. Jollys, J.V., Jollys, J.C., Wilson, J., Donovan, J., Nanchamel, K., and Abrams, P.: Does sexual ethuality extend to urinary symptoms? Neurourol. Urodyn., 391-392, 1993.

20. Chancellor, M.B. and Rivas, D.A.: American Urological Association symptom index for women without voiding symptoms: lack of index specificity for benign prostatic hyperplasia. J. Urol., 150: 1706-1708, 1993.

21. Lepor, H. and Machi, G.: Comparison of AUA symptom index in unselected males and females between fifty-five and seventy-nine years of age. Urol., 42: 36-40, 1993.

22. Abrams, P.: In support of pressure-flow studies for evaluating men with lower urinary tract symptoms. Urol., 44: 153-155, 1994.

23. Eckhardt, M.D., van Venrooij, G.E., van Melick, H.H., and Boon, T.A.: Prevalence and bothersomeness of lower urinary tract symptoms in benign prostatic hyperplasia and their impact on well-being. J. Urol., 166: 563-568, 2001.

24. Barry, M.J., Fowler, F.J., Jr., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L., Mebust, W.K., and Cockett, A.T.: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J. Urol., 148: 1549-1557, 1992.

25. Tsang, K.K. and Garraway, W.M.: Impact of benign prostatic hyperplasia on general well-being of men. Prostate, 23: 1-7, 1993.

26. Garraway, W.M., Armstrong, C., Auld, S., King, D., and Simpson, R.J.: Follow-up of a cohort of men with untreated benign prostatic hyperplasia. Eur. Urol., 24: 313-318, 1993.

27. Barry, M.J., Fowler, F.J., Jr., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L., and Mebust, W.K.: Measuring disease-specific health status in men with benign prostatic hyperplasia. The Measurement Committee of The American Urological Association. Med. Care, 33: AS145-AS155, 1995.

28. Garraway, W.M., Collins, G.N., and Lee, R.J.: High prevalence of benign prostatic hypertrophy in the community. Lancet, 338: 469-471, 1991.

29. Chute, C.G., Panser, L.A., Girman, C.J., Oesterling, J.E., Guess, H.A., Jacobsen, S.J., and Lieber, M.M.: The prevalence of prostatism: a population-based survey of urinary symptoms. J. Urol., 150: 85-89, 1993.

30. Norman, R.W., Nickel, J.C., Fish, D., and Pickett, S.N.: 'Prostate-related symptoms' in Canadian men 50 years of age or older: prevalence and relationships among symptoms. Br. J. Urol., 74: 542-550, 1994.

31. Bosch, J.L., Hop, W.C., Kirkels, W.J., and Schröder, F.H.: The International Prostate Symptom Score in a community-based sample of men between 55 and 74 years of age: prevalence and correlation of symptoms with age, prostate volume, flow rate and residual urine volume. Br. J. Urol., 75: 622-630, 1995.

32. Chatelain, Ch, Denis, L., Foo, J.K.T., Khoury, S., McConnell, J., and the members of the committees: Evaluation and treatment of lower urinary tract symptoms (LUTS) in older men. In: Benign Prostatic Hyperplasia. Edited by Denis, L., Griffiths, K. and Khoury, S. Fifth edition, Plymbridge distributors, Plymouth, UK, pp. 521-525, 2000.

33. Gisolf, K.W., van Venrooij, G.E., Eckhardt, M.D., and Boon, T.A.: Analysis and reliability of data from 24-hour frequency-volume charts in men with lower urinary tract symptoms due to benign prostatic hyperplasia. Eur. Urol., 38: 45-52, 2000.

34. Drach, G.W., Layton, T.N., and Binard, W.J.: Male peak urinary flow rate: relationships to volume voided and age. J. Urol., 122: 210-214, 1979.

35. International Scientific Committee: Recommendations of the evaluation and treatment of lower urinary tract symptoms (LUTS) suggestive of Benign Prostatic Obstruction. In: Proceedings of the fourth International Consultation on Benign Prostatic Hyperplasia. Edited by Denis, L., Griffiths, K. and Khoury, S. Plymbridge distributors, Plymouth, UK, pp. 669-684, 1998.

36. Reynard, J.M., Yang, Q., Donovan, J.L., Peters, T.J., Schäfer, W., de la Rosette, J.J., and Dabhoiwala, N.F.: The ICS-'BPH' study: uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction. Br. J. Urol., 83: 619-623, 1998.

37. Hinman, F., Jr. and Cox, C.E.: Residual urine volume in normal male subjects. J. Urol., 97: 641-645, 1967.

38. Eckhardt, M.D., van Venrooij, G.E., and Boon, T.A.: Symptoms, prostate volume and urodynamic findings in elderly male volunteers without and with LUTS and in patients with LUTS suggestive of benign prostatic hyperplasia. Urol., 58: 966-971, 2001.

39. Birch, N.C., Hurst, G., and Doyle, P.T.: Serial residual volumes in men with prostatic hypertrophy. Br. J. Urol., 62: 571-575, 1988.

40. Bruskewitz, R.C., Iversen, P., and Madsen, P.O.: Value of postvoid residual urine determination in evaluation of prostatism. Urol., 20: 602-604, 1982.

41. Abrams, P.H. and Griffiths, D.J.: The assessment of prostatic obstruction from urodynamic measurements and from residual urine. Br. J. Urol., 51: 129-134, 1979.

42. Griffiths, D., Höfner, K., van Mastrigt, R., Rollema, H.J., Spangberg, A., and Gleason, D.: Standardization of terminology of lower urinary tract function: pressure-flow studies of voiding, urethral resistance, and urethral obstruction. International Continence Society Subcommittee on Standardization of Terminology of Pressure-Flow Studies. Neurourol. Urodyn., 16: 1-18, 1997.

43. Schäfer, W.: Analysis of bladder-outlet function with the linearized passive urethral resistance relation, linPURR, and a disease-specific approach for grading obstruction: from complex to simple. World. J. Urol., 13: 47-58, 1995.

44. Schäfer, W.: Principles and clinical application of advanced urodynamic analysis of voiding function. Urol. Clin. North Am., 17: 553-566, 1990.

45. Roehrborn, C.G.: Accurate determination of prostate size via digital rectal examination and transrectal ultrasound. Urol., 51: 19-22, 1998.

46. Roehrborn, C.G., Girman, C.J., Rhodes, T., Hanson, K.A., Collins, G.N., Sech, S.M., Jacobsen, S.J., Garraway, W.M., and Lieber, M.M.: Correlation between prostate size estimated by digital rectal examination and measured by transrectal ultrasound. Urol., 49: 548-557, 1997.

47. Styles, R.A., Neal, D.E., and Powell, P.H.: Reproducibility of measurement of prostatic volume by ultrasound. Comparison of transrectal and transabdominal methods. Eur. Urol., 14: 266-269, 1988.

48. Juul, N., Torp-Pedersen, S., and Nielsen, H.: Abdominal ultrasound versus intravenous urography in the evaluation of infravesically obstructed males. Scand. J. Urol. Nephrol., 23: 89-92, 1989.

49. Stoevelaar, H.J., Van de Beek, C., Casparie, A.F., McDonnell, J., and Nijs, H.G.: Treatment choice for benign prostatic hyperplasia: a matter of urologist preference? J. Urol., 161: 133-138, 1999.

50. Wasson, J.H., Reda, D.J., Bruskewitz, R.C., Elinson, J., Keller, A.M., and Henderson, W.G.: A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. N. Engl. J. Med., 332: 75-79, 1995.

51. Lepor, H.: Alpha blockade in the therapy of benign prostatic hyperplasia. In: Prostate diseases. Edited by Lawson, R.K., WB Saunders, Philadelphia, USA, pp. 170-181, 1993.

52. Caine, M.: The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. J. Urol., 136: 1-4, 1986.

53. Lepor, H., Williford, W.O., Barry, M.J., Brawer, M.K., Dixon, C.M., Gormley, G., Haakenson, C., Machi, M., Narayan, P., and Padley, R.J.: The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. N. Engl. J. Med., 335: 533-539, 1996.

54. Narayan, P. and Tewari, A.: A second phase III multicenter placebo controlled study of 2 dosages of modified release tamsulosin in patients with symptoms of benign prostatic hyperplasia. United States 93-01 Study Group. J. Urol., 160: 1701-1706, 1998.

55. Buzelin, J.M., Roth, S., Geffriaud-Ricouard, C., and Delauche-Cavallier, M.C.: Efficacy and safety of sustained-release alfuzosin 5 mg in patients with benign prostatic hyperplasia. ALGEBI Study Group. Eur. Urol., 31: 190-198, 1997.

56. Martorana, G., Giberti, C., Di Silverio, F., von Heland, M., Rigatti, P., Colombo, R., Casadei, G., and Pacifico, P.: Effects of short-term treatment with the alpha 1-blocker alfuzosin on urodynamic pressure/flow parameters in patients with benign prostatic hyperplasia. Eur. Urol., 32: 47-53, 1997.

57. Wright, A.S., Thomas, L.N., Douglas, R.C., Lazier, C.B., and Rittmaster, R.S.: Relative potency of testosterone and dihydrotestosterone in preventing atrophy and apoptosis in the prostate of the castrated rat. J. Clin. Invest., 98: 2558-2563, 1996.

58. Grino, P.B., Griffin, J.E., and Wilson, J.D.: Testosterone at high concentrations interacts with the human androgen receptor similarly to dihydrotestosterone. Endocrinology, 126: 1165-1172, 1990.

59. Schröder, F.H., Westerhof, M., Bosch, R.J., and Kurth, K.H.: Benign prostatic hyperplasia treated by castration or the LH-RH analogue buserelin: a report on 6 cases. Eur. Urol., 12: 318-321, 1986.

60. Wu, J.P. and Gu, F.L.: The prostate 41-65 years post castration: An analysis of 26 eunuchs. Chinese medical journal, 100: 271-272, 1987.

61. Andersen, J.T., Ekman, P., Wolf, H., Beisland, H.O., Johansson, J.E., Kontturi, M., Lehtonen, T., and Tveter, K.: Can finasteride reverse the progress of benign prostatic hyperplasia? A two-year placebo-controlled study. The Scandinavian BPH Study Group. Urol., 46: 631-637, 1995.

62. Beisland, H.O., Binkowitz, B., Brekkan, E., Ekman, P., Kontturi, M., Lehtonen, T., Lundmo, P., Pappas, F., Round, E., Shapiro, D., et al: Scandinavian clinical study of finasteride in the treatment of benign prostatic hyperplasia. Eur. Urol., 22: 271-277, 1992.

63. Finasteride (MK-906) in the treatment of benign prostatic hyperplasia. The Finasteride Study Group. Prostate, 22: 291-299, 1993.

64. Gormley, G.J., Stoner, E., Bruskewitz, R.C., Imperato-McGinley, J., Walsh, P.C., McConnell, J.D., Andriole, G.L., Geller, J., Bracken, B.R., Tenover, J.S., Vaughan, E.D., Pappas, F., Taylor, A., Binkowitz, B., and Ng, J.: The effect of finasteride in men with benign prostatic hyperplasia. J. Urol., 167: 1102-1107, 2002.

65. McConnell, J.D., Bruskewitz, R., Walsh, P., Andriole, G., Lieber, M., Holtgrewe, H.L., Albertsen, P., Roehrborn, C.G., Nickel, J.C., Wang, D.Z., Taylor, A.M., and Waldstreicher, J.: The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. N. Engl. J. Med., 338: 557-563, 1998.

66. Andersen, J.T., Nickel, J.C., Marshall, V.R., Schulman, C.C., and Boyle, P.: Finasteride significantly reduces acute urinary retention and need for surgery in patients with symptomatic benign prostatic hyperplasia. Urol., 49: 839-845, 1997.

67. Moore, E., Bracken, B., Bremner, W., Geller, J., Imperato-McGinley, J., McConnell, J., Roy, J., Tenover, L., Vaughan, D., and Pappas, F.: Proscar: five-year experience. Eur. Urol., 28: 304-309, 1995.

68. Marberger, M.J., Andersen, J.T., Nickel, J.C., Malice, M.P., Gabriel, M., Pappas, F., Meehan, A., Stoner, E., and Waldstreicher, J.: Prostate volume and serum prostate-specific antigen as predictors of acute urinary retention. Combined experience from three large multinational placebo-controlled trials. Eur. Urol., 38: 563-568, 2000.

69. Guess, H.A., Chute, C.G., Garraway, W.M., Girman, C.J., Panser, L.A., Lee, R.J., Jacobsen, S.J., McKelvie, G.B., Oesterling, J.E., and Lieber, M.M.: Similar levels of urological symptoms have similar impact on Scottish and American men--although Scots report less symptoms. J. Urol., 150: 1701-1705, 1993.

70. Lowe, F.C.: Phytotherapy in the management of benign prostatic hyperplasia. Urol., 58: 71-76, 2001.

71. Lowe, F.C. and Fagelman, E.: Phytotherapy in the treatment of benign prostatic hyperplasia. Curr. Opin. Urol., 12: 15-18, 2002.

72. Buck, A.C.: Phytotherapy for the prostate. Br. J. Urol., 78: 325-336, 1996.

73. Wilt, T.J., Ishani, A., Stark, G., MacDonald, R., Lau, J., and Mulrow, C.: Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. JAMA, 280: 1604-1609, 1998.

74. Freyer, P.J.: A new method of performing prostatectomy. Lancet, 1: 774-775, 1900.

75. Freyer, P.J.: One thousand cases of total enucleation of the prostate for radical cure of enlargement of that organ. BMJ, 2: 868-870, 1912.

76. Millin, R.: Retropubic prostatectomy: New extravesical technique: Report on 20 cases. Lancet, 2: 693-696, 1945.

77. Meyhoff, H.H., Nordling, J., and Hald, T.: Clinical evaluation of transurethral versus transvesical prostatectomy. A randomized study. Scand. J. Urol. Nephrol., 18: 201-209, 1984.

78. Jenkins, B.J., Sharma, P., Badenoch, D.F., Fowler, C.G., and Blandy, J.P.: Ethics, logistics and a trial of transurethral versus open prostatectomy. Br. J. Urol., 69: 372-374, 1992.

79. Verdaasdonk, R.M., Borst, C., and van Gemert, M. J.: Explosive onset of continuous wave laser tissue ablation. Phys. Med. Biol., 35: 1129-1144, 1990.

80. Nesbit, R.M.: Transurethral prostatectomy. Rev. Mex. Urol., 35: 349-362, 1943.

81. Hopkins, H.H.: Optical principles of the endoscope. In: Endoscopy. Edited by Bercy, G., Appleton-Century-Crofts, New York, pp. 3-26, 1976.

82. Nesbit, R.M.: A history of transurethral prostatectomy. Rev. Mex. Urol., 35: 349-362, 1975.

83. Creevy, C.D. and Webb, E.A.: A fatal hemolytic reaction following transurethral resection of the prostate gland. Surgery, 21: 55-56, 1947.

84. Pearce, J.A.: Historical background. In: Electrosurgery. Chapman and Hall, London, UK, pp.1-15, 1986.

85. Honig, W.M.: The mechanism of cutting in electrosurgery. IEEE Biomed. Eng., 22: 58-62, 1975.

86. Mitchell, J.P. and Lumb, G.N.: Principles of surgical diathermy and its limitations. Br. J. Surg., 50: 314-320, 1962.

87. Ornstein, D.K., Rao, G.S., Smith, D.S., and Andriole, G.L.: The impact of systematic prostate biopsy on prostate cancer incidence in men with symptomatic benign prostatic hyperplasia undergoing transurethral resection of the prostate. J. Urol., 157: 880-883, 1997.

88. Horninger, W., Unterlechner, H., Strasser, H., and Bartsch, G.: Transurethral prostatectomy: mortality and morbidity. Prostate, 28: 195-200, 1996.

89. Mebust, W.K., Holtgrewe, H.L., Cockett, A.T., and Peters, P.C.: Transurethral prostatectomy: immediate and postoperative complications. Cooperative study of 13 participating institutions evaluating 3,885 patients. J. Urol., 141: 243-247, 1989.

90. Uchida, T., Ohori, M., Soh, S., Sato, T., Iwamura, M., Ao, T., and Koshiba, K.: Factors influencing morbidity in patients undergoing transurethral resection of the prostate. Urol., 53: 98-105, 1999.

91. Doll, H.A., Black, N.A., McPherson, K., Flood, A.B., Williams, G.B., and Smith, J.C.: Mortality, morbidity and complications following transurethral resection of the prostate for benign prostatic hypertrophy. J. Urol., 147: 1566-1573, 1992.

92. van Swol, C.F., van Vliet, R.J., Verdaasdonk, R.M., and Boon, T.A.: Electrovaporization as a treatment modality for transurethral resection of the prostate: influence of generator type. Urol., 53: 317-321, 1999.

93. Calkins, H., Langberg, J., Sousa, J., el Atassi, R., Leon, A., Kou, W., Kalbfleisch, S., and Morady, F.: Radiofrequency catheter ablation of accessory atrioventricular connections in 250 patients. Abbreviated therapeutic approach to Wolff-Parkinson-White syndrome. Circulation, 85: 1337-1346, 1992.

94. Rossi, S., Di Stasi, M., Buscarini, E., Cavanna, L., Quaretti, P., Squassante, E., Garbagnati, F., and Buscarini, L.: Percutaneous Radiofrequency Interstitial Thermal Ablation in the Treatment of Small Hepatocellular Carcinoma. Cancer J. Sci. Am., 1: 73, 1995.

95. Goldwasser, B., Ramon, J., Engelberg, S., Ohad, D., Sharkey, H., Strul, B., Rasor, J.S., and Edwards, S.D.: Transurethral needle ablation (TUNA) of the prostate using low-level radiofrequency energy: an animal experimental study. Eur. Urol., 24: 400-405, 1993.

96. Roehrborn, C.G., Issa, M.M., Bruskewitz, R.C., Naslund, M.J., Oesterling, J.E., Perez-Marrero, R., Shumaker, B.P., and Narayan, P.: Transurethral needle ablation for benign prostatic hyperplasia: 12-month results of a prospective, multicenter U.S. study. Urol., 51: 415-421, 1998.

97. Bruskewitz, R., Issa, M.M., Roehrborn, C.G., Naslund, M.J., Perez-Marrero, R., Shumaker, B.P., and Oesterling, J.E.: A prospective, randomized 1-year clinical trial comparing transurethral needle ablation to transurethral resection of the prostate for the treatment of symptomatic benign prostatic hyperplasia. J. Urol., 159: 1588-1593, 1998.

98. Perlmutter, A.P. and Perachino, M.: Mechanism of microwave thermotherapy. World J. Urol., 16: 82-88, 1998.

99. Yerushalmi, A., Fishelovitz, Y., Singer, D., Reiner, I., Arielly, J., Abramovici, Y., Catsenelson, R., Levy, E., and Shani, A.: Localized deep microwave hyperthermia in the treatment of poor operative risk patients with benign prostatic hyperplasia. J. Urol., 133: 873-876, 1985.

100. Servadio, C., Leib, Z., and Lev, A.: Diseases of prostate treated by local microwave hyperthermia. Urology, 30: 97-99, 1987.

101. Brehmer, M.: Morphological changes in prostatic adenomas after transurethral microwave thermotherapy. Br. J. Urol., 80: 123-127, 1997.

102. Bolmsjo, M., Wagrell, L., Hallin, A., Eliasson, T., Erlandsson, B.E., and Mattiasson, A.: The heat is on--but how? A comparison of TUMT devices. Br. J. Urol., 78: 564-572, 1996.

103. Bdesha, A.S., Schachter, M., Sever, P., and Witherow, R.O.: Radioligand-binding analysis of human prostatic alpha-1 adrenoreceptor density following transurethral microwave therapy. Br. J. Urol., 78: 886-892, 1996.

104. de la Rosette, J.J., Blute, M.L., and Desgrandchamp, F.: Transurethral thermotherapy using the Prostatron device. World J. Urol., 16: 89-95, 1998.

105. de la Rosette, J.J., Laguna, M.P., Gravas, S., and De Wildt, M.J.: Transurethral microwave thermotherapy: the gold standard for minimally invasive therapies for patients with benign prostatic hyperplasia? J. Endourol., 17: 245-251, 2003.

106. Floratos, D.L., Kiemeney, L.A., Rossi, C., Kortmann, B.B., Debruyne, F.M., and de la Rosette, J.J.: Long-term follow-up of randomized transurethral microwave thermotherapy versus transurethral prostatic resection study. J. Urol., 165: 1533-1538, 2001.

107. Minnee, P., Debruyne, F.M., and de la Rosette, J.J.: Transurethral microwave thermotherapy in benign prostatic hyperplasia. Curr. Urol. Rep., 1: 110-115, 2000.

108. Nau, W.H. jr., Milam, D.F., and Roseli, R.J.: Principles of laser surgery. In: Benign Prostatic Hyperplasia. Edited by Narayan, P., Churchill Livingston, London, UK, pp. 221-229, 2000.

109. McCullough, D.L., Roth, R.A., Babayan, R.K., Gordon, J.O., Reese, J.H., Crawford, E.D., Fuselier, H.A., Smith, J.A., Murchison, R.J., and Kaye, K.W.: Transurethral ultrasound-guided laser-induced prostatectomy: National Human Cooperative Study results. J. Urol., 150: 1607-1611, 1993.

110. Kabalin, J.N., Terris, M.K., Mancianti, M.L., and Fajardo, L.F.: Dosimetry studies utilizing the Urolase right-angle firing neodymium:YAG laser fiber in the human prostate. Lasers Surg. Med., 18: 72-80, 1996.

111. Costello, A.J., Bowsher, W.G., Bolton, D.M., Braslis, K.G., and Burt, J.: Laser ablation of the prostate in patients with benign prostatic hypertrophy. Br. J. Urol., 69: 603-608, 1992.

112. Anson, K., Nawrocki, J., Buckley, J., Fowler, C., Kirby, R., Lawrence, W., Paterson, P., and Watson, G.: A multicenter randomized prospective study of endoscopic laser ablation versus transurethral resection of the prostate. Urol., 46: 305-310, 1995.

113. Jung, P., Mattelaer, P., Wolff, J. M., Mersdorf, A., and Jakse, G.: Visual laser ablation of the prostate: efficacy evaluated by urodynamics and compared to TURP. Eur. Urol., 30: 418-423, 1996.

114. Cowles, R.S., Kabalin, J.N., Childs, S., Lepor, H., Dixon, C., Stein, B., and Zabbo, A.: A prospective randomized comparison of transurethral resection to visual laser ablation of the prostate for the treatment of benign prostatic hyperplasia. Urol., 46: 155-160, 1995.

115. Kingston, T.E., Nonnenmacher, A.K., Crowe, H., Costello, A.J., and Street, A.: Further evaluation of transurethral laser ablation of the prostate in patients treated with anticoagulant therapy. Aust. N. Z.J. Surg., 65: 40-43, 1995.

116. Kabalin, J.N. and Gill, H.S.: Urolase laser prostatectomy in patients on warfarin anticoagulation: a safe treatment alternative for bladder outlet obstruction. Urol., 42: 738-740, 1993.

117. McNicholas, T.A., Steger, A.C., and Bown, S.G.: Interstitial laser coagulation of the prostate. An experimental study. Br. J. Urol., 71: 439-444, 1993.

118. Muschter, R.: Interstitial laser therapy of benign prostatic hyperplasia. In: Urologic surgery. Edited by Graham, S.D. and Glenn, J.S., Lippincott-Raven, Philadelphia, USA, pp. 1111-1118, 1999.

119. Polepalle, S. and Monga, M.: Interstitial laser therapy for benign prostatic hyperplasia in the anticoagulated patient. Tech. Urol., 7: 285-287, 2001.

120. Gomella, L.G., Lotfi, M.A., Rivas, D.A., and Chancellor, M.B.: Contact laser vaporization techniques for benign prostatic hyperplasia. J. Endourol., 9: 117-123, 1995.

121. Keoghane, S.R. and Cranston, D.W.: Contact laser prostatectomy in anti-coagulated patients: mixed results. Br. J. Urol., 77: 613-614, 1996.

122. Mueller, E.J.: Contact laser vaporization of the prostate in patients on chronic anticoagulant therapy. Tech. Urol., 4: 156-159, 1998.

123. Dotter, C.T.: Transluminally-placed coilspring endarterial tube grafts. Long-term patency in canine popliteal artery. Invest. Radiol., 4: 329-332, 1969.

124. Fabian, K.M.: The interprostatic "partial catheter" (urologic spiral) II. Urologe A, 23: 229-233, 1984.

125. Chapple, C.R., Milroy, E.J., and Rickards, D.: Permanently implanted urethral stent for prostatic obstruction in the unfit patient. Preliminary report. Br. J. Urol., 66: 58-65, 1990.

126. Guazzoni, G., Montorsi, F., Coulange, C., Milroy, E., Pansadoro, V., Rubben, H., Sarramon, J. P., and Williams, G.: A modified prostatic UroLume Wallstent for healthy patients with symptomatic benign prostatic hyperplasia: a European Multicenter Study. Urol., 44: 364-370, 1994.

127. Williams, G. and White, R.: Experience with the Memotherm permanently implanted prostatic stent. Br. J. Urol., 76: 337-340, 1995.

128. de la Rosette, J.J., Beerlage, H.P., and Debruyne, F.M.: Role of temporary stents in alternative treatment of benign prostatic hyperplasia. J. Endourol., 11: 467-472, 1997.

129. Petas, A., Isotalo, T., Talja, M., Tammela, T.L., Valimaa, T., and Tormala, P.: A randomised study to evaluate the efficacy of a biodegradable stent in the prevention of postoperative urinary retention after interstitial laser coagulation of the prostate. Scand. J. Urol. Nephrol., 34: 262-266, 2000.

130. Petas, A., Talja, M., Tammela, T.L., Taari, K., Valimaa, T., and Tormala, P.: The biodegradable self-reinforced poly-DL-lactic acid spiral stent compared with a suprapubic catheter in the treatment of post-operative urinary retention after visual laser ablation of the prostate. Br. J. Urol., 80: 439-443, 1997.

CHAPTER 2

Correlations of urodynamic changes with changes in symptoms and well-being after transurethral resection of the prostate

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Abstract

Purpose: To establish the predictive value of urodynamics on the outcome of transurethral prostate resection for benign prostatic enlargement we correlated urodynamic changes with symptomatic improvement, decreased bother, and increased general well-being and quality of life after transurethral prostate resection.

Materials and Methods: Men with lower urinary tract symptoms were selected if they met study criteria and underwent tests recommended by the International Scientific Committee on Benign Prostatic Hyperplasia, and if post-void residual volume and prostate size were estimated. Patients answered quality of life, symptom index, symptom problem index and benign prostatic hyperplasia impact index questions. Patients also underwent urodynamic evaluation. Men were included in analysis when transurethral prostate resection was selected as treatment modality. Of the 132 patients included 93 were reevaluated 6 months after transurethral prostate resection.

Results: Improvements after transurethral prostate resection were significantly associated with decreased bladder outlet obstruction ($p<0.01$). However, 32 cases that were unobstructed or equivocal preoperatively also benefited moderately from resection. Effective capacity, that is cystometric capacity minus post-void residual urine volume, increased by an average of 45% postoperatively. The increase in effective capacity contributed to a significant decrease in symptoms and bother, and improved well-being. Of the men with a urodynamically proved stable bladder 90% maintained a stable bladder after prostatectomy, while in 50% with a urodynamically proved unstable bladder it became stable postoperatively.

Conclusions: Performing urodynamics preoperatively helps to predict the degree of symptom relief, decreased bother and increased well-being after transurethral prostate resection.

Introduction

Surgical treatment for prostatic enlargement associated with benign prostatic hyperplasia (BPH) is one of the most common operations performed in the modern western world. Using life table methods the lifetime probability of surgical treatment is estimated to be 29%.[1] Patients have a spectrum of symptoms that are currently referred to as lower urinary tract symptoms.[2] The International Scientific Committee (ISC) of the International Consultation on BPH recommends the quantitative documentation of symptom prevalence[3] using the International Prostate Symptom Scores (I-PSS) questionnaire and quality of life question developed by the Measurement Committee of the American Urological Association (AUA).[4]

In the past decision making in regard to treatment was mainly based on symptoms and the degree of bladder outlet obstruction. However, it was reported that the degree of outlet obstruction and prostate size were not associated with symptoms and quality of life.[5] Moreover, the degree of bother reported by the patient is not the same as the presence and frequency of symptoms.[6] Symptom bother and negative impact on quality of life are the main reasons that patients seek treatment for lower urinary tract symptoms.[7] Therefore, the AUA Measurement Committee developed and validated appropriate scores for quantifying lower urinary tract symptom bother. The committee introduced a symptom problem index with 7 bothers questions, of which each corresponds to a symptom question on I-PSS.[8] The committee also developed the BPH impact index, consisting of 4 questions on patient well-being and the social implications of lower urinary tract symptoms.[8]

The ISC recommends pressure flow studies for evaluating patients before invasive therapies or when a precise diagnosis of bladder outlet obstruction is important.[3] The outcome of therapy appears to be related to pretreatment urodynamic findings since patients with obstruction fare better than those without obstruction.[9] The urodynamics subcommittee of the ISC recommends filling cystometry and pressure flow studies.[9] The committee claims that performing preoperative urodynamics is cost-effective, allowing treatment to be directed toward the patients who are most likely to benefit. Cases that are unobstructed or equivocal can be managed by less expensive and less morbid therapies.

Bosch analyzed studies of the pretreatment and posttreatment values of relevant urodynamic parameters.[10] As he determined, the rank order of urodynamic efficacy shows a high level of agreement with the reported rank order of the symptomatic efficacy of various treatment modalities for decreasing urethral resistance. These analyses were performed at the grouplevel.

In our current study of men who underwent transurethral prostate resection we calculated improvement or worsening of a parameter in each individual by comparing the preoperative value with the value 6 months after resection. Symptomatic improvement, decreased bother, increased general well-being and quality of life were correlated with urodynamic changes to establish the relationship of the outcome of resection to pretreatment and posttreatment urodynamic findings.

Materials and methods

Men with lower urinary tract symptoms underwent basic initial evaluation (history, physical examination, digital rectal examination, urinalysis and renal function assessment) and recommended diagnostic tests (uroflowmetry and post-void residual urine estimation), conforming to the recommendations of the International Consensus Committee on BPH from 1993, as updated in 2000 by the ISC.[3] Men were eligible for study if they were older than 45 years old, had no exclusion criteria specified by the ISC,[3] post-void residual urine volume was estimated reliably and prostate size was determined by transrectal ultrasound. I-PSS[4] was completed by all men. The symptom index was calculated by summing the 7 scores. We introduced an additional question into the AUA symptom index on the frequency of daytime voiding, which was scored as: 0: 1 to 3 times, 1: 4 to 5 times, 2: 6 to 7 times, 3: 8 to 9 times and 4: 10 times or more. Each patient answered the quality of life question.[4] We included the 7 bother questions of the symptom problem index, of which each corresponds to a symptom question. The symptom problem index was calculated by summing the 7 scores.[8] We also included BPH impact index questions, consisting of 4 questions on patient well-being and the social implications of lower urinary tract symptoms.[8] The BPH impact index was calculated by summing the 4 scores.

All patients underwent filling cystometry and pressure-flow studies. Filling cystometry was performed with the patient supine and sitting. Pressure-flow studies were done twice with the patient sitting. Bladder pressure was recorded with a 5Fr catheter and rectal pressure was measured with a 14Fr catheter. Each was connected to an external pressure transducer. The bladder was filled with saline at 37 ^{0}C through a second 5Fr catheter at a constant rate of 50 ml. per minute. In some men an 8Fr double lumen catheter was used for bladder pressure measurement and bladder filling. Filling was stopped when the patient had a strong desire to void. The first pressure flow study was done with measuring and filling catheters in the bladder and the second study was done after removing the filling catheter. The pressure flow study with the lowest urethral resistance, usually during voiding with only the measuring catheter in the bladder, was used in further analysis.

The Schäfer obstruction grade,[11] urethral resistance factor[12] and Abrams-Griffiths number[13] were estimated from pressure flow studies. Cases with an obstruction grade of 0 or 1 were considered unobstructed, those with an obstruction grade of 2 were considered to be equivocal and those with an obstruction grade of 3 or greater were considered obstructed. Effective capacity was defined as cystometric capacity minus post-void residual urine volume. Men were included in analysis if they were selected for transurethral prostate resection, which was performed with a standard 24Fr resectoscope. As necessary, a suprapubic catheter was inserted perioperatively. All men were invited to participate in reevaluation 6 months after resection, including symptom, bother and problem index questions as well as filling cystometry and pressure flow studies.

We defined improvement or worsening of a urodynamic parameter in an individual as the ratio of the postoperative-to-preoperative value multiplied by 100%. Except for the Abrams-Griffiths number, Schäfer obstruction grade and contractility grade no urodynamic parameter could be 0 (table 1). We quantified improvement by considering a discrete parameter, such as the score on the symptom question, “Over the past month, how often have you had a weak urinary stream?” The score on that question was 0 to 5. The question arose whether improvement by treatment resulting in a decrease in a preoperative score of 5 to a postoperative score of 3 was equal to a decrease from 3 to 1. In our opinion the latter improvement is better. We developed for all discrete parameters (Schäfer obstruction grade, contractility grade and all scores) an improvement or worsening matrix, considering the different measures of improvement (see Appendix and table 6).

The Kolmogorov-Smirnov goodness of fit test was used to analyze whether the distribution of a variable was normal. Statistical analyses were performed with distribution free tests, including Kendall and Gibbons correlation method, Wilcoxon signed rank test and the Mann-Whitney U test. Two-tailed significance was considered at 0.05.

Results

In 39 of the 132 study participants (29%) follow-up after 6 months was not possible for various reasons (table 2).Table 1 lists baseline values in the remaining 93 men with a mean age plus or minus standard deviation of 65 ± 8 years (range 45 to 82) as well as postoperative values at 6 months. Of our 93 cases 32 were unobstructed or equivocal (Schäfer grade 1 or 2) and 61 were obstructed (Schäfer grade equal to 3 or higher). In the unobstructed and equivocal cases mean prostate volume was 36 ± 10 ml. and in the obstructed cases it was 48 ± 21 ml.

The almost 45% increase in mean effective capacity after transurethral prostate resection was due to the significant mean increase in cystometric capacity from 395 ±

Table 1 Preoperative characteristics and postoperative values together with significant differences.

Characteristic	Mean Preop. ± SD (range)		Mean Postop. ± SD (range)		p value
Max. free flow (ml/s)	11±4	(4-26)	23±10	(9-59)	<0.001
Detrusor pressure at max. flow (cm. water)	72±30	(32-200)	37±13	(17-80)	<0.001
Max. flow at pressure flow study (ml/s)	8±4	(1-18)	15±7	(2-37)	<0.001
Schäfer grade	3.2±1.3	(1-6)	1.0±0.9	(0-4)	<0.001
Abrams-Griffiths No.	57±33	(14-196)	7±21	(-51-76)	<0.001
Urethral resistance factor (cm water)	43±23	(18-161)	18±10	(5-72)	<0.001
Contractility degree	2.6±1.2	(0-5)	2.6±1.3	(0-5)	Not significant.
Cystometric capacity (ml)	395±145	(80-1000)	455±160	(170-950)	<0.001
Effective capacity (ml)	310±140	(30-660)	445±160	(150-920)	<0.001
Symptom Index	19±7	(5-34)	6±5	(0-26)	<0.001
Symptom problem index	14±8	(0-28)	3±5	(0-20)	<0.001
Quality of life	4.1±1.5	(1-6)	1.3±1.5	(0-6)	<0.001
BPH impact index	6.4±3.4	(0-13)	1.8±2.7	(0-12)	<0.001

Table 2 Reasons why 39 of 132 men were not followed at 6 months.

Reason	Number of patients
No agreement with further investigations	15
Patient condition did not allow reliable follow-up	8
Failed catheterization during urodynamic investigation at 6 months	5
Postoperative complications within 6 months.	4
Patient died within 6 months postoperatively	3
Patient. emigrated within 6 months postoperatively	4
Total number	39

145 to 455 ± 160 ml. and a concomitant decrease in post-void residual urine volume from 85 ± 120 to 10 ± 35 ml. Table 3 lists the Kendall and Gibbons correlation coefficients (Rs) of the improvement of urodynamic parameters versus all scores on I-PSS, BPH problem index, BPH impact index and quality of life questions. Men were excluded from analysis if preoperative and postoperative scores were 0, leading to different number of men for each score.

Improvement in obstruction grade, symptom index, symptom problem index, BPH impact index and quality of life were related to preoperative obstruction grade (table 4).Baseline values of the different categories of obstruction were not equal (table 4). There were significant correlations of baseline parameter values and improvements (symptom index R=0.25, quality of life R=0.38, symptom problem index R=0.35 and BPH impact index R=0.31, all p<0.01). Therefore, differences in baseline values affected improvement (table 4). The mean preoperative score on the symptom question of incomplete emptying in the 59 men with and 34 without post-void residual urine volume was 2.56 ± 1.83 and 2.59 ± 1.73, while average postoperative scores were 0.56 ± 1.00 and 0.68 ± 1.23, representing 60 ± 30% and 50 ± 55% mean improvement, respectively.

Table 5 lists improvements in the symptom index, symptom problem index, BPH impact index and quality of life in relation to preoperative and postoperative prevalence of urodynamically proved detrusor instability. Of the men 50 (54%) had a stable bladder preoperatively and the bladder remained stable 6 months after transurethral prostate resection in 45 (90%), while instability developed in 5 (10%). A total of 43 patients (46%) had an unstable bladder preoperatively, including 20 (47%) in whom bladder instability persisted postoperatively. Mean preoperative obstruction grade, mean maximum amplitude of instability, mean age, mean symptom index, mean symptom problem index, mean BPH impact index and mean quality of life score did not differ in men who maintained an unstable bladder (group 3) and those who achieved a stable bladder (group 1). The men in groups 1 and 2 showed significantly better improvement in the symptom index (p=0.02), BPH impact index (p=0.01) and quality of life (p=0.007) than those in whom an unstable bladder persisted (group 3) and in whom an unstable bladder developed postoperatively (group 4). The improvement in the symptom problem index was not significant (p=0.09). No significant differences in age was detected in the 4 groups.

Of our cases 9 (10%) were unobstructed preoperatively and 23 (25%) were equivocal. These patients also benefited from prostatectomy (table 4). In these 32 men mean effective capacity increased from 355 to 495 ml. The prevalence of

Table 3 Improvement in urodynamic parameters according to symptoms, problems, bother and quality of life.

	Number of patients	Urethral Resistance Factor (R)	p Value	Obstruction Grade (R)	p Value	Effective Capacity (R)	p Value
Symptoms							
Emptying	78	0.17	< 0.05	0.18	< 0.05	0.09	-
Frequency	92	0.15	< 0.05	0.10	-	0.16	< 0.05
Intermittency	78	0.17	< 0.05	0.21	< 0.05	0.06	-
Urgency	82	0.16	< 0.05	0.13	-	0.20	< 0.05
Weak stream	86	0.34	< 0.01	0.37	< 0.01	0.09	-
Hesitancy	67	0.38	< 0.01	0.38	< 0.01	0.09	-
Nocturia	93	0.21	< 0.01	0.19	< 0.05	0.14	-
I-PSS	93	0.32	< 0.01	0.29	< 0.01	0.20	< 0.05
Daytime voiding frequency	93	0.26	< 0.01	0.20	< 0.05	0.21	< 0.01
Problems							
Emptying	72	0.24	< 0.01	0.25	< 0.01	0.13	-
Frequency	75	0.23	< 0.01	0.22	< 0.01	0.12	-
Intermittency	72	0.33	< 0.01	0.29	< 0.01	0.01	-
Urgency	84	0.14	-	0.16	< 0.05	0.16	< 0.05
Weak stream	75	0.31	< 0.01	0.28	< 0.01	0.04	-
Hesitancy	66	0.40	< 0.01	0.36	< 0.01	0.06	-
Nocturia	73	0.31	< 0.01	0.28	< 0.05	0.18	< 0.05
Problem index	91	0.31	< 0.01	0.31	< 0.01	0.12	-
Bother							
Physical discomfort	80	0.33	< 0.01	0.32	< 0.01	0.15	-
Health worry	77	0.24	< 0.01	0.22	< 0.01	0.06	-
Overall worry	90	0.25	< 0.01	0.25	< 0.01	0.12	-
No normal activity	50	0.28	< 0.01	0.27	< 0.01	0.31	< 0.01
Impact index	93	0.24	< 0.01	0.26	< 0.01	0.12	-
Quality of life	93	0.30	< 0.05	0.27	< 0.05	0.22	< 0.05

Table 4 Improvement in Schäfer obstruction grade, symptom index, problem index, BPH impact index and quality of life in relation to preoperative obstruction grade.

Preop. Grade	Number of Patients	Av. % Grade Improve-ment	Preoperative Symptom Index (% improvement)	Preoperative Problem Index (% improvement)	Preoperative BPH Impact Index (% improvement)	Preoperative Quality of Life (% improvement)
1	9	15	16.1 (40)	10.3 (38)	9.2 (43)	3.3 (42)
2	23	30	17.4 (45)	12.4 (52)	10.1 (50)	3.7 (44)
3	23	50	17.5 (48)	13.0 (64)	9.8 (55)	4.2 (49)
4	18	56	21.7 (60)	17.5 (70)	12.2 (61)	4.6 (61))
5	17	64	19.8 (63)	13.5 (58)	9.7 (58)	3.9 (55)
6	3	83	28.0 (64)	22.3 (92)	15.3 (95)	5.3 (87)

No patient had a preoperative obstruction grade of 0.

Table 5 Postoperative improvement according to instability.

	Group 1	Group 2	Group 3	Group 4
Number of patients	23	45	20	5
Mean age ± SD	66.8±6.6	63.6±8.6	67.7±7.9	65.6±7.2
Bladder				
Preop.	Unstable	Stable	Unstable	Stable
Postop.	Stable	Stable	Unstable	Unstable
Symptom index				
Mean preop. ± SD	19.4±5.6	18.0±6.8	20.4±5.2	18.8±8.8
Mean postop. ± SD	4.8±5.0	5.2±3.9	9.6±3.2	7.8±6.7
% Improvement	61	54	37	47
Problem index				
Mean preop. ± SD	13.1±7.4	13.6±7.2	15.1±8.2	14.6±10.9
Mean postop. ± SD	2.4±4.4	2.4±3.4	5.4±6.0	5.0±4.7
% Improvement	65	65	47	32
BPH impact index				
Mean preop. ± SD	6.4±3.3	5.9±3.2	7.3±3.6	6.6±3.6
Mean postop. ± SD	1.0±2.1	1.2±1.8	3.6±3.7	2.0±3.0
% Improvement	67	59	39	45
Quality of life				
Mean preop. ± SD	4.0±1.5	4.0±1.5	4.3±1.6	4.2±1.5
Mean postop. ± SD	1.0±1.4	1.1±1.3	2.0±1.5	2.2±1.6
% Improvement	62	55	39	34

instability decreased from 35% to 16% and the prevalence of post-void residual urine volume from 55 to 20%. The mean decrease was 2.4 to 1.4 for nocturia, 2.6 to 1.3 for frequency and 2.2 to 0.8 for urgency, while mean symptom problem scores on these symptoms decreased from 1.8 to 0.8, 2.1 to 0.5 and 2.2 to 0.8, respectively.

Discussion

Of our 132 study participants 39 (29%) were not followed at 6 months for various reasons (table 2). Of these 39 men 15 were satisfied with the results of transurethral prostate resection but did not agree to further investigations. In 8 patients the health condition did not allow investigation at 6 months since 1 had cancer, 2 had dementia, 1 had renal insufficiency requiring dialysis, 2 had bladder stones and 2 had neurological complaints. In 5 men catheterization failed, including 2 with bladder neck stenosis, 1 who did not agree to further investigation and 2 with a maximum free flow rate of 15 and 25 ml. per second, respectively. In these latter 2 men catheterization may have failed due to the sometimes large space created in the prostatic urethra by transurethral resection. Another 4 patients had postoperative complications within 6 months, of whom 1 underwent repeat transurethral prostate resection and 3 underwent subsequent surgery for urethral stricture.

In the 93 men evaluated the mean maximum flow rate and mean maximum detrusor pressure at maximum flow before and after operation were similar to those in the literature (table 1).[14-16] The mean AUA symptom index in our group decreased from 19 to 6 by 6 months after prostatectomy, similar to the reported decrease from 17.6 to 7.4 by 4 weeks.[4] Also, the preoperative symptom problem and BPH impact scores were similar to those reported by Barry et al.[8] Of the 93 cases evaluated 32 were unobstructed or equivocal. Nevertheless, mean prostate volume in these men was 36 ml. This finding shows that not only prostatic obstruction, but also prostatic enlargement was important in the treatment decision.

Table 3 shows slight differences in the R of the urethral resistance factor (continuous variable) with other parameters and the R of obstruction grade (discrete variable) with other parameters. This difference indicates that the variation resulting from the difference in the definition of improvement of a continuous variable and that of improvement of a discrete variable had minor importance. The Abrams-Griffiths number is less suited for our type of improvement grading because the number can have a negative value. Because most parameters did not show a normal distribution, only distribution-free tests were used.

Table 3 also shows that improved symptoms, decreased problems, decreased bother impact and improved quality of life were significantly associated with improved bladder outlet function. Men with high urethral resistance preoperatively benefit most from bladder outlet obstruction relief. Table 3 shows an R of 0.18 to 0.38 for improvement in voiding symptoms, which is higher than the R of 0.10 to 0.19 for improvement in storage symptoms in relation to the decrease in obstruction. These differences were not noted for the bother score.

Prostatectomy resulted in 45% increased effective capacity. The increase in bladder capacity 6 months after prostatectomy has been previously observed by Meyhoff et al.[17] The increase in effective bladder capacity was of the same order as the reported decrease in effective capacity during the development of benign prostatic obstruction.[18] Increased effective capacity significantly correlates with improvement in symptom frequency, urgency and voiding frequency in the daytime (table 3). Increased effective capacity results in decreased bother in regard to urgency, nocturia and trouble with normal activity. Increased effective capacity results in significantly better quality of life. Considering that urgency and nocturia are the most bothersome symptoms[6] and frequency is strongly associated with well-being[6], we conclude that the observed increase in effective capacity contributed to a significant decrease in bother and improvement in well-being.

Men with no obstruction preoperatively or in equivocal condition also benefited moderately from prostatectomy (table 4). In table 4 the improvements are not each listed in ascending order, which partly may have been due to differences in the baseline values of the various obstruction grade categories. Because of the significant correlations of baseline values with improvement after transurethral prostate resection, the significant correlations of obstruction grade improvement with symptom index, symptom problem index, BPH impact index and quality of life that are shown in table 3 are masked in table 4. The benefit of prostatectomy in unobstructed and equivocal cases may be explained by the resulting mean increase in effective capacity from 355 to 495 ml. and decrease in the prevalence of instability from 35% to 16%. After prostatectomy scores for the symptoms of nocturia, frequency and urgency, and associated symptom problems were strongly decreased. It is likely that irritative effects not due to bladder outlet obstruction cause symptoms in benign prostatic enlargement cases.

The decrease in post-void residual urine volume contributed significantly to the increase in effective capacity. Nevertheless, the feeling of incomplete emptying preoperatively and subjective improvement in emptying after prostate resection had no relationship with actual post-void residual urine volume and actual improvement in bladder emptying. Of preoperatively stable bladders 90% remained stable. It is unclear whether instability developed in the remaining 10% of bladders after prostatectomy or existing instability was missed preoperatively. About 50% of unstable bladders become stable after prostatectomy. However, which bladder becomes stable cannot be predicted preoperatively from symptoms, bother or urodynamic findings.

The disappearance of preoperative detrusor overactivity was not related to age. Men with a stable bladder preoperatively were younger than those with an unstable bladder, although the difference was not significant (p=0.06). Overall the group of men with a stable bladder after prostatectomy showed slightly higher but significant improvement in symptom score, BPH impact index and quality of life (table 5). Men with a stable bladder preoperatively are more likely to have a stable bladder after prostatectomy than those with an unstable bladder preoperatively.

Conclusions

Improved symptoms, decreased symptom problems, decreased impact of bother and improved quality of life are significantly associated with improved bladder outlet function. However, men who do not have obstruction preoperatively or are in equivocal condition also benefit from resection. The feeling of incomplete emptying preoperative and subjective improvement in emptying after prostate resection have no relationship with actual post-void residual urine volume and actual improvement in bladder emptying. However, a notable increase in effective bladder capacity partly caused by improved bladder emptying after transurethral prostate resection contributes to a significant decrease in symptoms and bother, and to improved well-being.

About 50% of the unstable bladders become stable after prostatectomy. Men with a stable bladder after prostatectomy show greater improvement in symptoms, the BPH impact index and quality of life than those with an unstable bladder postoperatively. Most preoperatively stable bladders remain stable but which unstable bladder may become stable after resection cannot be predicted. Performing preoperative urodynamics helps to predict the degree of symptom relief, decrease in bother and increase in well-being resulting from transurethral prostate resection.

Appendix

Quantification of the improvement by treatment of a discrete parameter such as the score on the symptom question “Over the past month, how often have you had a weak urinary stream?” needs some attention. The score on that question may vary from 0 to 5. The question arises whether improvement (Imp) by treatment resulting in a decrease of the preoperative score (pre) of 5 to a postoperative score (post) of 3 is equal to a decrease from 3 to 1. In our opinion the latter improvement is better. Applying the formula:

Imp = (pre-post)/(pre+post)

considers these differences in improvement. However, according to this formula, improvement from 5 to 0 is the same as improvement from 1 to 0. This result is obviated by adding 1 to each score, leading to the formula:

Imp = (pre+1-post-1) / (pre+1+post+1)

We wanted improvement to be 100% when the preoperative value was the maximum score (max), whereas the postoperative value was the minimum score (min). This result can be achieved by modifying the formula, that is

Imp = 100% x [(pre+1-post-1)/(pre+1+post+1)] x [(max+1+min+1)/(max+1-min-1)]

In the example of the weak urinary stream it leads to an improvement or worsening matrix (table 6). A score of 0 means that the symptom is absent. A preoperative score and a postoperative score of 0 cannot be interpreted in terms of improvement or worsening. Similar matrixes can be developed for the Schäfer obstruction grade, quality of life, symptom bother scores.

Table 6 Improvement or worsening matrix. The horizontal axis shows the preoperative score and the vertical axis shows the postoperative score.

pre = post =	**0**	**1**	**2**	**3**	**4**	**5**
0	1	47%	70%	84%	93%	100%
1	- 47%	0%	28%	47%	60%	70%
2	- 70%	-28%	0%	20%	35%	47%
3	- 84%	- 47%	- 20%	0%	16%	28%
4	- 93%	- 60%	- 35%	- 16%	0%	13%
5	-100%	- 70%	- 47%	- 28%	- 13%	0%

1. A score of 0 means that the symptom is absent. A preoperative score and a postoperative score of 0 cannot be interpreted in terms of improvement or worsening.

References

1. Glynn, R.J., Campion, E.W., Bouchard, G.R. and Silbert, J.E.: The development of benign prostatic hyperplasia among volunteers in the Normative Aging Study. Am. J. Epidemiol. 121: 78, 1985.

2. Abrams, P.: New words for old: lower urinary tract symptoms for "prostatism". BMJ 308: 929, 1994.

3. Recommendations of the International Scientific Committee 2001. In: Benign Prostatic Hyperplasia; 5th International Consultation on Benign Prostatic Hyperplasia (BPH). Edited by C. Chatelain, L. Denis, K.T. Foo, S. Khoury and J. McConnell. Plymouth United Kingdom: Plymbridge Distributors, pp. 519-534, 2001.

4. Barry, M.J., Fowler, F.J., Jr., O'Leary, M.P., Bruskewitz,R.C., Holtgrewe, H.L., Mebust, W.K. et al: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J. Urol. 148: 1549, 1992.

5. Eckhardt, M.D., van Venrooij, G.E. and Boon, T.A.: Symptoms and quality of life versus age, prostate volume, and urodynamic parameters in 565 strictly selected men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Urol. 57: 695, 2001.

6. Eckhardt, M.D., van Venrooij, G.E., van Melick, H.H. and Boon, T.A.: Prevalence and bothersomeness of lower urinary tract symptoms in benign prostatic hyperplasia and their impact on well-being. J. Urol. 166: 563, 2001.

7. Speakman, M.J.: Who should be treated and how? Evidence-based medicine in symptomatic BPH. Eur. Urol., suppl., 36: 40, 1999.

8. Barry, M.J., Fowler, F.J., Jr., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L. and Mebust, W.K.: Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of the American Urological Association. Med, Care,suppl., 33: AS145, 1995.

9. Abrams, P., Griffiths, D., Höfner, K. et al.: The urodynamic assessment of lower urinary tract symptoms. In: Benign Prostatic Hyperplasia. 5th International Consultation on Benign Prostatic Hyperplasia (BPH). Edited by C. Chatelain, L. Denis, K.T. Foo et al.: Plymouth, United Kingdom: Plymbridge Distributors, pp. 227-281, 2001.

10. Bosch, J.L.: Urodynamic effects of various treatment modalities for benign prostatic hyperplasia. J. Urol. 158: 2034, 1997.

11. Schäfer, W.: Analysis of bladder-outlet function with the linearized passive urethral resistance relation, linPURR, and a disease-specific approach for grading obstruction: from complex to simple. World J. Urol. 13: 47, 1995.

12. Griffiths, D., van Mastrigt, R. and Bosch, R.: Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size reduction on urethral obstruction due to benign prostatic hyperplasia. Neurourol. Urodyn. 8: 17, 1989.

13. Lim, C.S. and Abrams, P.: The Abrams-Griffiths nomogram. World J. Urol. 13: 34, 1995.

14. Meyhoff, H.H., Nordling, J. and Hald, T.: Urodynamic evaluation of transurethral versus transvesical prostatectomy. A randomized study. Scand. J. Urol. Nephrol. 18: 27, 1984.

15. Hellström, P., Lukkarinen, O. and Kontturi, M.: Bladder neck incision or transurethral electroresection for the treatment of urinary obstruction caused by a small benign prostate? A randomized urodynamic study. Scand. J. Urol. Nephrol. 20: 187, 1986.

16. Jensen, K.M., Jørgensen, J.B. and Mogensen, P.: Urodynamics in prostatism. I. Prognostic value of uroflowmetry. Scand. J. Urol. Nephrol. 22: 109, 1988.

17. Meyhoff, H.H., Gleason, D.M. and Bottaccini, M.R.: The effects of transurethral resection on the urodynamics of prostatism. J. Urol. 142: 785, 1989.

18. Eckhardt, M.D., van Venrooij, G.E. and Boon, T.A.: Interactions between prostate volume, filling cystometric estimated parameters, and data from pressure flow studies in 565 men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Neurourol. Urodyn. 20: 579, 2001.

CHAPTER 3

Comparison of outcomes of transurethral prostate resection in urodynamically obstructed versus selected urodynamically unobstructed or equivocal men

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Abstract

Objectives: To compare the benefits of TURP in urodynamically obstructed versus selected urodynamically unobstructed or equivocal men with severe lower urinary tract symptoms (LUTS) associated with benign prostatic enlargement.

Methods: In this case series study, men with LUTS were selected if they met study criteria and underwent the tests recommended by the International Scientific Committee on Benign Prostatic Hyperplasia. They also underwent urodynamic investigations. Men were included when TURP was selected as the treatment modality. Of the 132 included subjects, 93 could be re-evaluated 6 months after surgery.

Results: Of the 93 re-evaluated men, 59 were obstructed and 34 unobstructed or equivocal. Both groups were similar with respect to age, symptoms, bother, BPH-impact index, and quality of life. The quantified reductions in symptoms and bother in the unobstructed and equivocal men were about 70% of those reductions in obstructed men. In the equivocal men, and even in the unobstructed men, a significant reduction with 40% of the urethral resistance occurred.

Conclusions: TURP may be a good treatment alternative for unobstructed or equivocal men with severe LUTS associated with prostatic enlargement, who opt for resection or who do not respond to or do not tolerate medical therapy.

Introduction

The number of patients with lower urinary tract symptoms (LUTS)[1] suggestive of benign prostatic hyperplasia (BPH) will strongly increase because of an ageing population. In addition, the number of treatment modalities is increasing. These changes make patient selection at baseline more and more critical.

The International Scientific Committee (ISC) of the International Consultation on BPH[2] recommends the quantitative documentation of symptom prevalence using the International Prostate Symptom Scores (I-PSS) questionnaire and quality of life question developed by the Measurement Committee of the American Urological Association (AUA).[3] This Measurement Committee also developed and validated a symptom problem index (SPI) with 7 bother questions each of which corresponds to a symptom question of I-PSS,[4] and the BPH impact index (BII), consisting of 4 questions on patient well-being and the social implications of lower urinary tract symptoms.[4]

The relationships among urodynamic parameters, treatment outcome, symptom relief and patient satisfaction, are still the subject of controversy. The ISC recommends pressure flow studies before invasive therapies or when a precise diagnosis of bladder outlet obstruction is important.[2] The outcome from therapy appears to be related to the pretreatment urodynamic findings, because patients with obstruction fare better than those without obstruction.[5] Therefore, less expensive and less morbid therapies are recommended for patients who are unobstructed or equivocal. The use of alpha-blockers in these men has increased strongly. A concomitant decrease in transurethral prostatectomy has been observed.

Men with high urethral resistance preoperatively benefit most from bladder outlet obstruction relief.[6] Nevertheless, men who were preoperatively unobstructed or equivocal also benefited significantly from transurethral resection of the prostate.[6] This is especially important for unobstructed or equivocal men with severe LUTS associated with prostatic enlargement who opt for resection, who do not respond to medical therapy and/or in whom adverse effects require medication discontinuation.

The aim of this study was to compare the quantified improvements six months after transurethral prostatectomy in unobstructed and equivocal men with severe LUTS associated with prostatic enlargement, with the outcomes of transurethral prostatectomy in obstructed men with prostatic enlargement.

Material and methods

All men, who are older than 45 years of age and visiting our outpatient department with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH), undergo a basic initial evaluation and tests conforming to the recommendations of the International Consensus Committee on BPH from 1993 as updated in 2000 by the ISC.[2] Their residual volume is estimated and their prostate size is determined by transrectal ultrasound. I-PSS, quality of life, bother, and BPH impact index questions are completed by all men. In our outpatient department it is common practice to perform filling cystometry and pressure flow studies in all of these men.

On the basis of the pressure-flow measurements men are classified as unobstructed, equivocal or obstructed according to the provisional International Continence Society method for the definition of obstruction.[7] In addition the urethral resistance factor [8] (URA) is estimated. Effective capacity is defined as the cystometric capacity minus the post-void residual urine volume.

Different treatment modalities for LUTS owing to prostatic enlargement are available in our clinic: watchful waiting, medical therapy and surgery (abdominal and transurethral prostate resection, electrovaporization and laser therapy).

On the basis of the results of the investigations and the results of any previous treatment, the treatment alternatives are discussed by the staff of the department of urology with each patient. Generally surgery is advised in urodynamically obstructed normal risk men. In urodynamically equivocal and unobstructed men generally medication with alpha-blockers is usually advised. The final decision about the treatment modality is the result of a shared process between the patient and his medical attendant taking into account the benefits and the risks of treatment alternatives.

From 1995 on we investigated the effects of different kinds of transurethral prostate surgery. All normal risk men who had no exclusion criteria specified by the ISC[2] and who are considered for transurethral surgery are invited to participate in follow-up studies. After obtaining the informed consent, a re-evaluation 6 months after surgery was performed, including symptoms, quality of life, bother and problem index questions as well as filling cystometry and pressure-flow study. Between 1996 and 2002 men were included in the present study if transurethral resection of the prostate (TURP) was the treatment modality. Except for prostate size (see discussion), no statistically significant differences between these men and the men undergoing other types of transurethral surgery were detected (table 1). Because some parameters are not normally distributed, the median value (50th percentile) and the 25th and 75th percentiles are listed.

We calculated improvement or worsening of a parameter by comparing the postoperative value (*Vpost)* to the preoperative value (*Vpre)*. If an increase in the value *V* of the parameter was expected (for instance free flow rate) the improvement was defined as: *Vpost-Vpre*. If a reduction in the value was expected (for instance URA) the improvement was defined as : *Vpre-Vpost.*

The Kolmogorov-Smirnov goodness of fit test was used to analyze whether the distribution of a variable was normal. Statistical analyses were performed with

Table 1 Baseline values in the enrolled group (n=132) versus those in the other groups undergoing transurethral surgery (n=109).

Parameter	Other men (n=109)			Enrolled men (n=132)			Mann-Whitney U test
	25th	50th (median)	75th	25th	50th (median)	75th	P-value
Age (years)	59	66	74	58	66	71	0.7
Prostate volume (ml)	28	35	46	30	40	51	0.02
Maximal free flow rate (ml/s)	8	10	14	7	10	13	0.9
Residual volume (ml)	0	35	170	0	55	140	0.5
Cystometric capacity (ml)	250	400	500	300	350	500	0.8
Effective capacity (ml)	200	290	400	200	295	400	0.9
Urethral resistance factor URA) (cm H_2O)	28.6	36.6	47.0	29.0	40.0	57.8	0.08
I-PSS	15	20.5[1]	24	13	19	25	0.5
Quality of life score	3	4	5	3	4	5	0.5
Symptom problem index	8	13.5[1]	18	8	13.5	20	0.9
BPH impact index	4	6	8	3	6	8	0.9

1. Because of a high number of equal values some percentiles are not integers.

distribution free tests, including the Fisher-Irwin test for two-by-two tables, the Wilcoxon signed rank test and the Mann-Whitney *U* test. Two-tailed significance was considered at 0.05.

Results

In 39 men of the prospectively selected 132 patients (43 equivocal or unobstructed and 89 obstructed) follow-up at 6 months was not possible: 15 men, were satisfied but did not agree to additional investigations; in 8 men, condition did not allow reliable follow-up; in 5, catheterization failed at follow-up urodynamic investigation; 4 men had postoperative complications; 3 men had died; and 4 men emigrated within 6 months after operation. Of the 39 men in whom follow-up was not possible 30 were

obstructed and 9 were equivocal or unobstructed. Of the 93 men included for analysis, 59 were obstructed, 28 equivocal and 6 unobstructed. The reasons why equivocal or unobstructed men underwent resection were: 13 men opted for resection, 12 men could not benefit from or did not tolerate alpha-blockers, and in 5 men high post-void urine volumes were found. Four men underwent resection for different reasons.
Except for urethral resistance factor (URA), no statistically significant differences were found between the baseline values of the 28 equivocal men and those of the 6 unobstructed men. In table 2, the baseline values of the equivocal or unobstructed men are compared to those of the obstructed men.

Table 2 Baseline values of unobstructed and equivocal men (n=34) versus obstructed men (n=59).

Parameter	**Unobstructed and equivocal men** (n=34)			**Obstructed men** (n=59)			Mann-Whitney U test
	25th	50th (median)	75th	25th	50th (median)	75th	P-value
Age (years)	58	66	71	60	66	72	0.7
Prostate volume (ml)	28	34	44	33	46	60	<0.01
Maximal free flow rate (ml/s)	9.9	11.7	15.5	6	9	12	<0.01
Residual volume (ml)	0	23	85	0	50	120	0.3
Cystometric capacity (ml)	300	400	585	300	350	450	0.07
Effective capacity (ml)	250	325	500	200	270	380	0.02
Urethral resistance factor (URA) (cm H_2O)	20.6	25.2	31.5	39.1	46.0	62.1	<0.01
I-PSS	12	18	21.25	16	20	25	0.04
Quality of life score	2	4	5	3	5	5	0.03
Symptom problem index	4.75	11	19	10	15	21	0.08
BPH impact index	3	6,5	8.25	4	6	9	0.9

A large similarity was found between both groups, although statistically significant differences were also found. The baseline values (table 2) of the 9 equivocal or unobstructed men who did not undergo the six-month follow-up examinations did not differ significantly from those of the 34 equivocal or unobstructed followed-up men included in the study. Except for the quality of life score, the baseline values of the 30 obstructed men who did not undergo the six-month follow-up examinations also did not differ significantly from those of the 59 obstructed men. The quality of life score

was significantly (p=0.03) greater (quality of life was lower) in the study men (see discussion).
In table 3, improvements six months after transurethral resection in the equivocal or unobstructed group are compared to those in the obstructed group

Table 3 Improvements in unobstructed and equivocal men (n=34) versus those in the obstructed men (n=59).

Parameter	**Unobstructed and equivocal men** (n=34)			**Obstructed men** (n=59)			Mann-Whitney *U* test
	25th	50th (median)	75th	25th	50th (median)	75th	P-value
URA reduction (cm H_2O)	4.9	9.5	13.2	21.5	30.3	46.4	<0.001
Maximal free flow rate increase (ml/s)	2.0	7.8	12.6	6.0	11.0	18.0	0.02
Cystometric capacity increase (ml)	-25	50	150	-50	50	150	0.7
Effective capacity increase (ml)	0	130	220	50	120	200	0.6
Reduction in symptom index	5	10	13.25	9	14	21	0.02
Reduction in symptom bother index	2	7	14.75	6	11	18	0.04
Reduction in quality of life score	1	2	4	2	3	4	0.03
Reduction in BPH impact index	1.75	3.5	7	2	4	7	0.2

Except for obstruction grade and maximal free flow rate, the changes were very similar in both groups. In the obstructed men the median value of URA decreased from 46.0 to 15.0 cm water (p<0.001), in the equivocal group from 27.9 to 16.2 (p<0.001) and in the small group of 6 unobstructed men from 19.2 to 11.8 (p=0.03).
No significant differences at all of improvements between the 6 unobstructed men and the 28 equivocal men could be detected. The different reasons why resection was performed in the equivocal and unobstructed men did not cause different postoperative benefits.
In all 6 unobstructed men URA decreased after prostatectomy. In 4 men of the equivocal group, URA worsened after prostatectomy and in 2 men of the obstructed group. The parameters in table 3 were recalculated after exclusion of these men. The differences with the values in table III appear to be marginal.
Of the 59 obstructed men, 32 (54%) had an unstable bladder preoperatively and 19 (32%) postoperatively. Of the 34 equivocal or unobstructed men, 11 (32%) had an unstable bladder preoperatively and 6 (17%) postoperatively. No significant

difference between the decrease in prevalence of unstable bladders in both groups was observed.
Of the 59 obstructed men, 27 (46%) had a residual volume higher than 50 ml preoperatively and 2 (3%) postoperatively. Of the 34 equivocal or unobstructed men, 13 (38%) had a postvoid residual volume greater than 50 ml preoperatively and 3 (9%) postoperatively. Again, no statistically significant difference between the groups could be detected.

Comment

Physicians are rather reserved about resection of the prostate in equivocal or unobstructed men. A problem arises when a man with considerable LUTS and benign prostatic enlargement but without infravesical obstruction does not want medication at all, does not benefit from medication or does not tolerate this treatment. The results of our prospective study showed that our selected equivocal or unobstructed men were similar to our obstructed group with respect to age, symptoms, bothering, BPH-index, quality of life, prevalence of post-void residual volume and prevalence of unstable bladder (table 2 and results). Their prostate volume was smaller but still significantly enlarged (table 2). Most of these men opted for surgery, did not benefit from medication or did not tolerate medication. These different reasons did not result in different post-operative benefits.
In the obstructed group the median value of URA significantly decreased by 70%, in the equivocal group by 40% and even in the small unobstructed group significantly by 40%. Thus, prostatectomy in equivocal and unobstructed men can result in a significant reduction in outflow resistance.
The reductions in symptom and bother in the equivocal and unobstructed men were approximately 70% of those in the obstructed men (table 3). Also, the post-void residual urine volume and the prevalence of detrusor instability decreased after prostatectomy in the equivocal and unobstructed men.
Baseline values of our enrolled men did not differ from those of the men selected for other transurethral surgical procedures, except for prostate size (Table 1). This difference can be explained by the exclusion of men for electrovaporization and laser prostatectomy in our clinic when prostate volume was more than 65 ml. This exclusion also explains the (not statistically significant) greater URA in our enrolled group (Table 1). In the present study 13 men (all obstructed) had a prostate volume greater than 65 ml. This introduced bias; however the bias was in favor of the obstructed group because differences between the obstructed men and the equivocal or unobstructed men were more pronounced.
A large number of men (39 out of 132) could not followed-up. This may have caused bias. However, the baseline values of the equivocal or unobstructed men without

follow-up did not differ from those who had follow-up. The same applied for the obstructed groups. The proportion of men without follow-up was (p=0.10, not-significant) smaller in the equivocal or unobstructed group compared to the obstructed group. Men who had real obstruction benefited more than those who were equivocal or unobstructed and therefore may have been more satisfied. Of the 15 men who were satisfied but did not agree to additional investigations, 12 appeared to be obstructed preoperatively. This proportion was greater than would be expected from the pre-operative distribution, but the difference was not significant (p=0.25).

Alpha-blockers are the most frequently used prescription medication.[9] Witjes et al.[10] evaluated clinical and urodynamic changes in men with and without bladder outlet obstruction after six months of terazosin treatment. Although the inclusion and exclusion criteria differed slightly, the baseline values in their groups correspond to those in our groups. In our obstructed men, symptom reduction and increase of quality of life appeared to be more pronounced after prostate resection than the changes in their obstructed men treated with terazosin. Our urodynamic improvements after prostate resection even appeared to be superior to their urodynamic improvements after terazosin treatment. In the equivocal or unobstructed men, symptom reduction and increase of quality of life after terazosin treatment appeared to be comparable to those in our equivocal or unobstructed men after prostate resection. However urodynamic improvements after prostate resection appeared to be superior to those after terazosin treatment.

The number of men treated with alpha-blocker therapy is increasing. However, not all men can benefit enough from such medication[11] and some men opt for resection or show adverse effects.

Even though some bias may exist (negatively and positively) in our unobstructed or equivocal men who opt for resection, who did not respond to medical therapy and/or in whom adverse effects were associated with treatment discontinuation, prostate resection appeared to be a good treatment alternative.

The presence or absence of urethral obstruction in men with lower urinary tract symptoms associated with prostatic enlargement should not be the decisive factor in treatment choice and absence of obstruction should not be an exclusion criterion for transurethral prostate resection. Nevertheless, decision-making remains a shared process between the physician and patient, taking into account the benefits and risks (mortality and morbidity) involved in the treatment alternatives.

Conclusions

Equivocal or unobstructed men with severe LUTS associated with benign prostatic enlargement may benefit fairly from transurethral prostatectomy compared with obstructed men. Therefore, the presence or absence of urethral obstruction in men with LUTS associated with prostate enlargement should be a less-decisive factor in the treatment choice. Transurethral resection may be a good treatment alternative for selected equivocal or unobstructed men who opt for resection, who do not respond to medical therapy, and/or in whom adverse effects require treatment discontinuation. Transurethral resection can result in a significant reduction in the urethral resistance, even in unobstructed men.

References

1. Abrams, P.: New words for old: lower urinary tract symptoms for “prostatism”. BMJ 308: 929-930, 1994.

2. Recommendations of the International Scientific Committee: Evaluation and treatment of lower urinary tract symptoms (LUTS) in older men, in Chatelain, C., Denis, L., Foo, K.T., Khoury, S., McConnell, J. (Eds.): Benign Prostatic Hyperplasia; 5th International Consultation on Benign Prostatic Hyperplasia (BPH). Plymouth, UK, Plymbridge Distributors, 2001, pp 519-534.

3. Barry, M.J., Fowler, F.J. Jr, and O’Leary, M.P.: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J. Urol. 148: 1549-1557, 1992.

4. Barry, M.J., Fowler, F.J. Jr, and O’Leary, M.P., et al: Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. Med. Care 33 (4 Suppl): AS145-155, 1995.

5. Abrams, P., Griffiths, D., and Höfner, K., et al: The urodynamic assessment of lower urinary tract symptoms, in Chatelain, C., Denis, L., Foo, K.T., Khoury, S., McConnell, J. (Eds.): Benign Prostatic Hyperplasia; 5th International Consultation on Benign Prostatic Hyperplasia (BPH). Plymouth, UK, Plymbridge Distributors, 2001, pp 227-281.

6. Van Venrooij, G.E., Van Melick, H.H., and Eckhardt, M.D., et al: Correlations of urodynamic changes with changes in symptoms and well-being after transurethral resection of the prostate. J. Urol. 168: 605-609. 2002.

7. Griffiths, D.J., Höfner, K., and van Mastrigt, R., et al: Standardization of terminology of lower urinary tract function: pressure-flow studies of voiding, urethral resistance and urethral obstruction. Neurourol. Urodyn. 16: 1-18, 1997.

8. Griffiths, D., van Mastrigt, R., and Bosch, R.: Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size reduction on urethral obstruction due to benign prostatic hyperplasia. Neurourol. Urodyn. 8: 17-27, 1989.

9. Wilt, T.J., Howe, W., and MacDonald, R.: Terazosin for treating symptomatic benign prostatic obstruction: a systematic review of efficacy and adverse effects. BJU Int 89: 214-225, 2002.

10. Witjes, W.P., Rosier, P.F., and Caris, C.T., et al: Urodynamic and clinical effects of terazosin therapy in symptomatic patients with and without bladder outlet obstruction: a stratified analysis. Urol. 49: 197-205, 1997.

11. Holtgrewe, H.L.: Current trends in management of men with lower urinary tract symptoms and benign prostatic hyperplasia. Urol. 51(4A Suppl):1-7, 1998

CHAPTER 4

A randomized controlled trial comparing transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia: urodynamic effects

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Abstract

Purpose: We compared urodynamic and flowmetry improvements in men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) after transurethral resection of the prostate (TURP), contact laser prostatectomy and electrovaporization (EVAP; Vaportrode).

Materials and Methods: A prospective randomized controlled trial was performed. Included were men with LUTS suggestive of BPH who met the criteria of the International Scientific Committee on BPH, had a prostate volume of between 20 and 65 ml and a Schäfer's obstruction grade ≥2. Before and six months after treatment, urodynamics and free flowmetry were performed.

Results: Fifty men were randomized for TURP, 45 for laser treatment and 46 for EVAP. Baseline characteristics were similar in the different treatment groups. Detrusor contractility did not change in any of the treatment groups. The average maximum free flow rate increased by a factor of 2.4 after TURP, 2.5 after laser prostatectomy and 2.4 after EVAP. Schäfer's obstruction grade decreased by a factor of 0.3 in all groups. Obstruction (Schäfer grade >2) was not noted after TURP or EVAP, but it was evident in 2 patients after laser prostatectomy. Effective capacity increased by a factor of 1.5 or more. The incidence of detrusor instability was decreased by half in all groups. The incidence of significant post-void residual urine volume decreased in all groups.

Conclusions: There were no significant differences in the improvements of urodynamic and uroflowmetry parameters six months after treatment when comparing TURP, contact laser prostatectomy and electrovaporization in men with LUTS suggestive of BPH.

Introduction

Increased life expectancy causes an increase in the number of men presenting with lower urinary tract symptoms (LUTS), which is often associated with benign prostatic hyperplasia (BPH). An increasing number of these men are treated with pharmacotherapy, such as alpha-blockers, although a large population still requires surgical treatment[1]. For several decades transurethral prostate resection (TURP) has been the gold standard for surgical therapy. However, this procedure is associated with a mortality rate of 0.23% within 30 days of the operation[2], increasing to 2.8% during 12 months of follow-up[3]. The immediate postoperative morbidity rate is 18%[2] and still 12% between 6 and 12 months postoperatively[3]. These rather high percents have led to many attempts to introduce new methods that match the benefits of TURP, but show a lower mortality and morbidity rate.

In 1992 the use of laser therapy for BPH was introduced[4]. Several interstitial, contact and non-contact laser types were used and contact laser prostatectomy showed good results[5]. In 1993 another promising new treatment modality, namely electrovaporization (EVAP), was introduced[6]. These new techniques use extreme heat to vaporize prostatic tissue and leave behind a layer of coagulated tissue.

Several trials comparing the outcome of different treatment methods were performed in the past. An extensive investigation of the urodynamic effects of various treatment modalities for BPH was described in the review of Bosch[7]. However, literature about randomized controlled trials comparing the urodynamic effects of new treatment modalities for BPH is rather scarce. We performed a randomized controlled trial in which we compared the urodynamic effects of contact laser therapy, EVAP and the gold standard, TURP, in men with LUTS suggestive of BPH. These effects were studied by filling cystometry and pressure-flow studies before and six months after treatment, and by free uroflowmetry before and several times after treatment for up to 12 months.

Materials and Methods

This prospective randomized controlled study was performed between 1996 and 2001 at the department of urology at our institution. Included were men older than 45 years old with LUTS suggestive of BPH. All patients underwent a history, digital rectal examination, transrectal ultrasonography, urodynamic evaluation, free uroflowmetry, post-void residual volume estimation, urinalysis and blood analysis. Questionnaires concerning symptom score (International prostate symptom score (I-PSS))[8], Quality of life[8] and bother score (Symptom Problem Index)[9], morbidity and sexuality were completed before and several times after surgery. In study patients prostate volume was between 20 ml and 65 ml and the Schäfer obstruction grade was 2 or higher. Patients with any exclusion criteria of the International Consensus Committee on BPH were excluded from analysis[10].

Urodynamic studies consisted of filling cystometry and pressure-flow studies. Urodynamics were done before and 6 months after treatment. From the pressure-flow studies, the obstruction grade (0: no obstruction, to 6: severe obstruction) and detrusor contractility (0: very weak, to 5: strong bladder), as proposed by Schäfer[11], were estimated, as well as the URA (group specific urethral resistance factor)[12]. Residual urine was estimated by catheterization. Effective bladder capacity was defined as maximum cystometric capacity (bladder filling at strong desire) minus residual volume. Uroflowmetry studies were also done before treatment and they were repeated 1 and 6 weeks and 3, 6 and 12 months after treatment. Flowmetry results were only included if patients voided more than 150 ml.

TURP was performed with a standard 24 Fr resectoscope, using glycine for irrigation. When necessary, a suprapubic catheter was inserted intraoperatively. Laser prostatectomy was performed with an SLT Nd:YAG laser (Surgical Laser Technologies, Oaks, Pennsylvania, USA) with an MTRL 10, 6.0 x 5.0 mm sapphire-tipped probe. A Morgenstern scope was used to introduce the glassfiber with the contact probe. Isotonic salt solution was used as the irrigation fluid. EVAP was performed with a Vaportrode (Circon-Acmi, Stanford, Connecticut USA) element using glycine for irrigation. All patients intravenously received antibiotics perioperatively and a 20 Fr transurethral catheter was placed postoperatively.

To calculate group size, we hypothesized that after 6 months laser prostatectomy resulted in 85% and EVAP in 70% of the increase in maximum flow (Qmax,free) due to TURP. Power was set at 90% and 2-sided significance was considered at 5%. As the standard deviation (SD) 4.6 ml/s for Qmax,free was selected since this SD was reported[13] in a similar group of men. We assumed a SD of 4.0 ml/s for the difference in Qmax,free. Using one-way ANOVA this resulted in group size of 32 men. This number is in agreement with the American Urological Association new technology assessment committee, which stated that more than 30 patients per group should be evaluated[14].

The Kolmogorov-Smirnov goodness-of-fit test was used to examine whether a variable was distributed normally. A number of parameters are reported with the SD since this convention is often followed in literature. Statistical analysis were done with one-way-ANOVA, the Kruskal-Wallis non-parametric test of independent variables and the Mann-Whitney *U* test.

Results

Table 1 lists the baseline characteristics of the study patients. There were no statistically significant differences among the three treatment groups in any parameter, except effective capacity and symptom score between TURP and Vaportrode patients (p=0.007 and p=0.04 respectively).
Table 2 shows maximum free flow estimated by free flowmetry. It was our intent to perform flowmetry before treatment and at several times after treatment up to twelve months. However, only at the pretreatment and six month points were sufficient patients evaluated to enable for statistically significant calculations (see discussion). There was no statistically significant difference in the increase of maximum flow among the groups after six months, on the Kruskal-Wallis non-parametric test of independent variables. Change is calculated as the ratio of posttreatment maximum flow after six months divided by pretreatment maximum flow. The average of these individually calculated changes is presented with the minimum and maximum change. In the TURP and laser groups there was always an increase in maximum free flow (minimum ratio >1.0). Three patients in the EVAP group showed a decrease in maximum flow (including one each from 12 to 8 ml/s, 15 to 12 ml/s and 15 to 11 ml/s).
The International Consultation on BPH[15] recommends standard criteria for efficacy of BPH treatment. Efficacy is graded as excellent for ΔQmax (change in maximum flow) ≥10 ml/s, good if 5≤ ΔQmax <10 ml/s, fair if 2.5≤ ΔQmax <5 ml/s and poor if ΔQmax <2.5 ml/s. Using these criteria, TURP, laser and EVAP were scored as: excellent in 65%, 69% and 59%, good in 21%, 31% and 21%, fair in 6%, 0% and 3% and poor in 9%, 0% and 17% of patients, respectively. A graphical representation is shown in figure 1.
About 30% of all included patients per group were not reexamined by urodynamics six months after treatment. Table 3 lists the reasons. Table 4 shows some urodynamic findings in the remaining men at baseline and six months after treatment. Change was again expressed as the average of all individually calculated ratios of posttreatment outcome divided by pretreatment outcome. Statistical analysis using one-way-ANOVA revealed no significant differences in the changes of all urodynamic parameters among the three treatment groups.
The data showed that the average detrusor pressure at maximum flow was decreased by half and that there was never an increase in detrusor pressure. The decrease in detrusor pressure was significant in all treatment groups, while contractility did not change significantly. The Schäfer discrete obstruction grade and continuous URA decreased significantly. A graphical representation is shown in figure 2. As mentioned in the materials and methods section, only patients

Table 1 Baseline characteristics of the 3 treatment groups (averages ± standard deviations).

	TURP	**Contact Laser**	**Vaportrode**
Number of patients included	50	45	46
Mean age (years) (range)	66 ± 8 (50-82)	67 ± 9 (49-82)	64 ± 10 (49-81)
Prostate Volume (ml)	37 ± 11	37 ± 11	35 ± 11
Maximum Free Flow (ml/s)	11 ± 4	12 ± 4	11 ± 4
Detrusor Pressure at Qmax (cm H_2O)	76 ± 27	69 ± 24	75 ± 26
Schäfer Obstruction Grade	3 ± 1	3 ± 1	3 ± 1
URA (cm H_2O)	43 ± 20	41 ± 23	45 ± 24
Effective Capacity (ml)	350 ± 140	300 ± 135	290 ± 145
Detrusor Instability (prevalence)	44%	48%	33%
Relative Residue >10% (prevalence)	46%	48%	59%
Symptom Score	16.8 ± 6.0	18.9 ± 6.8	20.2 ± 6.6
Bother Score	11.9 ± 6.7	12.5 ± 7. 8	14.1 ± 6.7
Quality of Life Score	3.8 ± 1.5	3.7 ± 1.6	4.1 ± 1.4

Table 2 Results of uroflowmetry (averages in ml/s ± standard deviations).

	Pre	week 1	week 6	month 3	**Month 6**	**Change**[1]	month 12
TURP	11 ± 4 n=46	18 ± 7 n=15	24 ± 12 n=16	25 ± 11 n=15	24 ± 7 n=37	2.4 (1.1– 6.4)[2] n=34	21 ± 8 n=11
Laser	11 ± 4 n=39	14 ± 7 n=11	20 ± 4 n=8	23 ± 11 n=12	24 ± 7 n=33	2.5 (1.4 – 6.0)[2] n=29	22 ± 11 n=11
Vaportrode	11 ± 4 n=41	17 ± 10 n=12	22 ± 7 n=13	20 ± 10 n=19	23 ± 10 n=33	2.4 (0.7 – 5.8)[2] n=29	23 ± 8 n=9

1. Average of all individually calculated changes (posttreatment value/ pretreatment value).
2. Range: this shows the minimum and maximum change. Change was calculated only in patients who underwent pre and posttreatment uroflowmetry.

Table 3 Reasons why included patients were not evaluated urodynamically after six months.

	TURP	Contact laser	Vaportrode
Peroperative and postoperative reasons up to one month			
Procedure during surgery changed for medical reasons	0	3	2
Equipment failure during surgery resulting in standard therapy (TURP)	-	2	1
Postoperative complications within one month	2	1	0
Surgery cancelled due to other (medical) problems	1	0	1
Procedure during surgery not correctly performed	0	0	4
Postoperative reasons after one month up to six months			
No agreement with re-examinations	2	4	3
Condition of patient did not allow reliable follow-up	3	3	2
Failed catheterization during urodynamics at six months	3	0	1
Postoperative complications within six months after surgery	2	0	0
Patient died within six months after surgery	2	0	0
Patient emigrated within six months after surgery	1	0	0

With a Schäfer grade of 2 or greater were included. The incidence of patients with a preoperative Schäfer grade of 2 or greater who were also examined at six months was 71% for TURP, 66% for laser and 81% for EVAP. In the TURP group all patients showed a decrease in Schäfer grade, including 94% who were unobstructed after TURP (Schäfer grade 0 or 1). Only two patients were equivocal (Schäfer grade 2). The Schäfer grade had been 5 and 4 before surgery respectively.In the laser group all except one patient had a decrease in Schäfer grade. In the laser group, 91% was unobstructed after laser therapy. The Schäfer grade increased from 4 to 5 in one patient, decreased from 4 to 3 in a second patient and from 3 to 2 in a third patient. In the Vaportrode group all except two patients had a decrease in Schäfer grade. These two patients showed no change with a Schäfer grade of 2 (equivocal). Of all patients who underwent electrovaporization 72% were unobstructed, while Vaportrode, while the remaining 28% became (or staid: 2 patients) equivocal. Thus, no patients were obstructed after Vaportrode.

Effective capacity is the maximum cystometric volume during urodynamics minus the residual volume after voiding. There was a significant increase in all three groups. It was highest in the Vaportrode group, although not significantly different from the other treatment modalities. Increase in effective capacity was the result of an increase in cystometric capacity and a concomitant decrease in residual volume. A graphical representation is shown in figure 3.

We also calculated the percent of patients with a clinically relevant post-void residual volume of more than 10% of maximum cystometric capacity. In all groups, especially the TURP group, a large decrease in that percent was demonstrated. The prevalence of detrusor instability was calculated in each group. For this calculation all patients with measurable instability were included, as recommended by the International Consultation on BPH. The number of patients was decreased by half in all three groups after treatment.

Table 5 shows the pre and posttreatment values for the symptom score index, symptom problem index (bother score) and the Quality of Life question. All changes were significant in all groups. There were no significant differences in changes among the three treatment modalities.

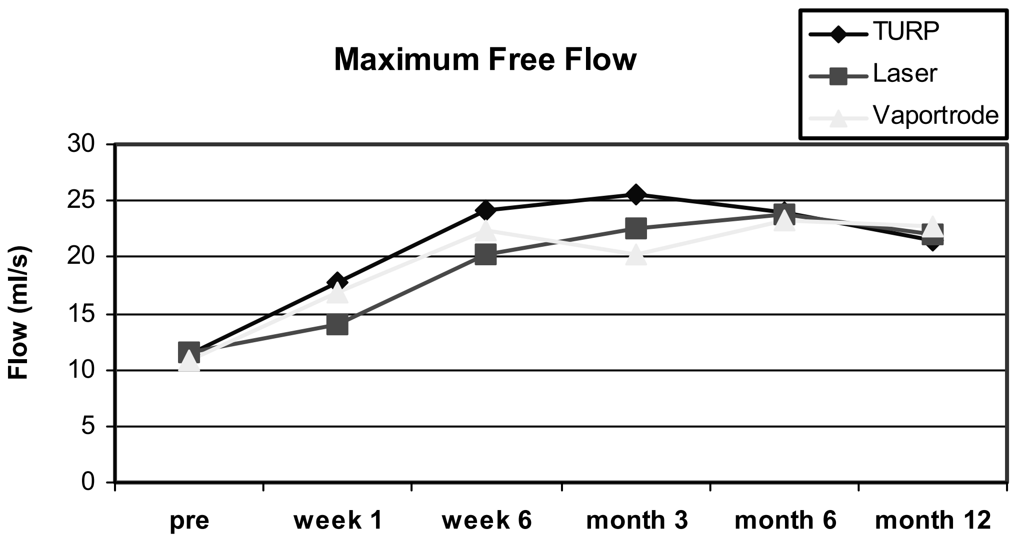

Figure 1 Mean maximum free urinary flow rate at baseline (pre) and at different time intervals for up to 12 months postoperatively for the three modalities.

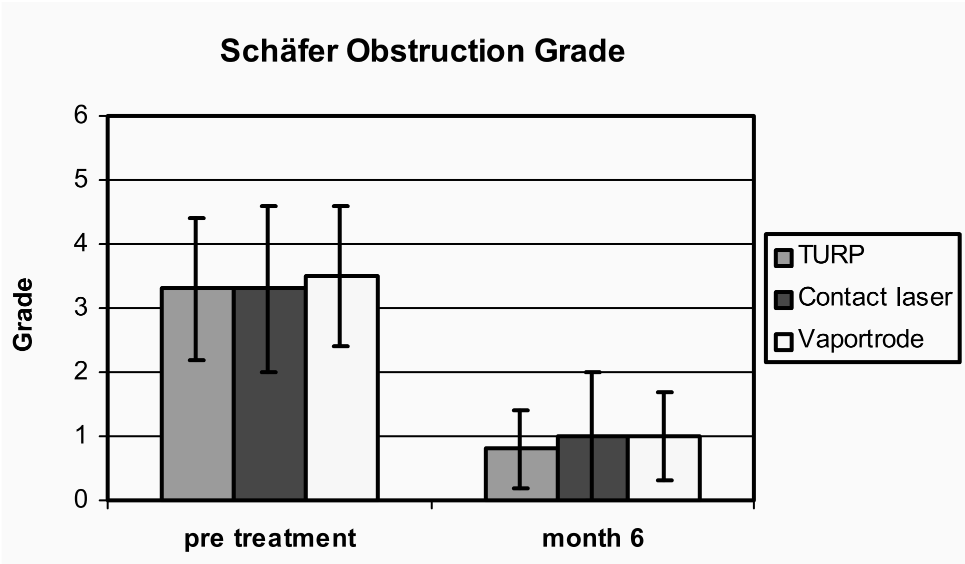

Figure 2 Mean Schäfer obstruction grade at baseline and 6 months postoperatively for the three modalities.

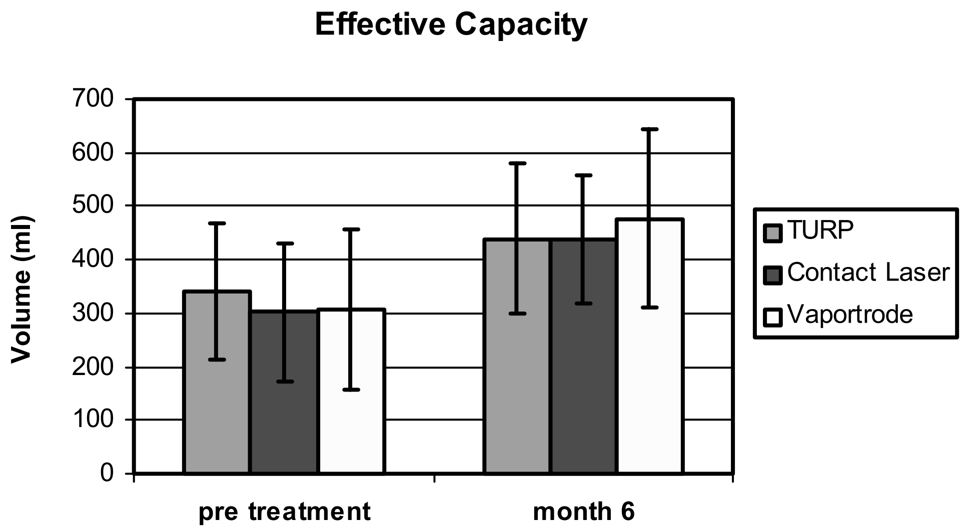

Figure 3 Effective capacity (defined as the maximum cystometric capacity minus post void residual urine volume) at baseline and 6 months postoperatively for the three modalities.

Table 4 Results of the urodynamic evaluations. Results only for patients who were evaluated pre and posttreatment: for TURP n=34, for Contact Laser n=32 and for Vaportrode n=32. (averages ± standard deviations).

Urodynamic parameter	Pretreatment	6 months Posttreatment	Change[1]	Range[2]
pQmax (cm H_2O)				
TURP	72 ± 26	33 ± 10	0.5	0.2 – 1.0
Laser	70 ± 24	37 ± 12	0.6	0.2 – 1.0
Vaportrode	78 ± 27	40 ± 13	0.5	0.2 – 1.0
Contractility				
TURP	2.4 ± 0.9	2.6 ± 1.3	1.2	0.5 – 3.0
Laser	2.3 ± 0.9	2.5 ± 1.0	1.2	0.3 – 3.0
Vaportrode	2.8 ± 1.2	2.8 ± 1.4	1.0	0.0 – 2.5
Schäfer grade				
TURP	3.3 ± 1.1	0.8 ± 0.6	0.3	0.0 – 0.5
Laser	3.3 ± 1.3	1.0 ± 1.0	0.3	0.0 – 1.3
Vaportrode	3.5 ± 1.1	1.0 ± 0.7	0.3	0.0 – 1.0
URA (cm H_2O)				
TURP	41 ± 20	14 ± 5	0.4	0.1 – 1.1
Laser	43 ± 26	17 ± 13	0.5	0.1 – 1.7
Vaportrode	46 ± 28	16 ± 6	0.4	0.1 – 1.0
Effective Capacity (ml)				
TURP	340 ± 125	440 ± 140	1.5	0.6 – 4.2
Laser	300 ± 130	435 ± 120	1.5	0.7 – 2.8
Vaportrode	305 ± 150	475 ± 165	2.1	0.6 – 8.2
Relative Residual Volume >10%[3]				
TURP	47%	3%		
Laser	41%	16%		
Vaportrode	32%	13%		
Detrusor Instability[3]				
TURP	47%	21%		
Laser	44%	22%		
Vaportrode	31%	16%		

1. Average of all individually calculated ratios (post-treatment value/ pre-treatment value).

2. Range shows the minimum and maximum change.

3.Prevalence.

Table 5 Changes in Symptom Score, Bother Score and Quality of Life (averages ± standard deviations).

Score	Pretreatment	6 months Posttreatment	Change[1]
Symptom Score			
TURP	16.8 ± 6.0	5.3 ± 5.1	0.32
Laser	18.9 ± 6.8	6.6 ± 5.8	0.35
Vaportrode	20.2 ± 6.6	7.2 ± 6.7	0.36
Bother Score			
TURP	11.9 ± 6.7	2.1 ± 4.2	0.18
Laser	12.5 ± 7.8	2.8 ± 4.4	0.22
Vaportrode	14.1 ± 6.7	3.5 ± 4.6	0.25
Quality of Life			
TURP	3.8 ± 1.5	0.9 ± 1.2	0.24
Laser	3.7 ± 1.6	± 1.1	0.30
Vaportrode	4.1 ± 1.4	1.6 ± 1.6	0.39

1. Average of all individually calculated changes (posttreatment/ pretreatment value).

Discussion

In three different ways heat is applied to remove the excess prostate tissue that causes LUTS. The gold standard, TURP, uses an electrically heated bent wire. Electricity flows from the active element (the electrode placed in the urethra) to the return electrode, which is a large surface electrode attached to the patient skin. In TURP there is a high current density over a small wire, resulting in tissue dissection and minimal coagulation[16]. When vessel cutting occurs, additional coagulation is necessary. Removed chips of prostatic tissue can be weighed and sent for pathological examination.

Electrovaporization uses the same principle as TURP, but the area over which electricity flows is much larger, which causes vaporresection with a layer of high-impedant-coagulated tissue a few millimeters thick. There are no chips of tissue that can be weighed or sent for pathological examination. Each method uses glycine, an electrically conductive fluid, as irrigation fluid with the potential risk of TUR syndrome.

A review of Patel et al[17] of EVAP included a meta-analysis of the first five prospectively randomized studies of this modality compared with loop resection. Only Hammadeh[18] compared TURP with the same EVAP element as in our study. The 3-year follow-up confirmed that EVAP was as effective as TURP for moderate BPH.

The urodynamic effect was not evaluated. The increase in Qmax (to more than 22 ml/s) is comparable to our results and this result was maintained after 3 years. After that time there was even a significant difference compared with TURP patients, in which average Qmax was lower (18 ml/s).

Laser prostatectomy can be performed in different ways. There is interstitial laser ablation in which a glassfiber is inserted into the prostate at fixed points. It causes necrosis and slow tissue sloughing for several weeks, making long catheterization necessary. Side fire laser prostatectomy is a non-contact laser technique in which laser light is deflected at a right angle at the end of the tip, causing mainly deep coagulation and some vaporization of prostate tissue. Contact laser prostatectomy uses a rounded black tip at the end of a glassfiber. Laser light energy is completely absorbed by the tip and transformed into heat. Direct contact of the tip with prostate tissue causes vaporization and coagulation, resulting in immediate tissue ablation.
In the Oxford laser prostate trial, Keoghane et al[19] studied extensively contact laser prostatectomy (identical device as in the present study) against TURP. They treated 72 patients by contact laser and 76 by TURP. They presented no urodynamic findings. TURP results for Qmax after one year are comparable to ours (11 at baseline to 21 ml/s), but their laser results are worse (12 to 17 ml/s). No significant change was observed in change in Qmax after one year. Peri-operative blood loss and transfusion rate were significantly lower for the laser group.

Tukhanen et al[20] compared also contact laser prostatectomy (same element as in the present study) with TURP in prostates smaller than 40 ml. In both groups 25 patients were evaluated with flowmetry and urodynamics among other parameters. After 3 and 6 months there were no significant changes between TURP and laser treatment for Qmax, detrusor pressure at Qmax and post-void residuals. Pre- and post-operative values are similar to the present study.

All laser techniques can be performed in saline, which should protect against the risk of TUR syndrome. Pathological examination is not possible.
Table 3 lists the reasons why patients were not evaluated urodynamically six months after surgery. The new methods rarely suffered from technical problems making cross-over to TURP necessary. One contact tip broke and once the laserdevice failed due to software problems. Bleeding was the main reason for changing the surgical procedure making coagulation with a rollerball necessary. In the Vaportrode group, four patients were not treated according to the protocol, making evaluation impossible. Catheterization at the second urodynamic study never failed in the laser group, though this happened once in the Vaportrode group and three times in the TURP group. This might be caused by the sometimes large TURP space that is created.

Significance for Qmax was tested using the Kruskal-Wallis non-parametric test of independent variables. Repeated measurements were not used because a marked drop-out of results at week 1, week 6, month 3 and month 12 had occurred. An average of about 30% of the patients in all groups were evaluated at these intervals. A large variation in the increase between the different treatment groups made one-way-ANOVA not suitable.

Symptomatic improvement was obvious in all groups, but there were no significant differences in changes between the different modalities. Data are equal to those seen in the above mentioned studies[18-20], although they do not provide information about change in bother score. A detailed evaluation of symptomatic and subjective changes in time is in preparation.

Conclusions

Urodynamic and flowmetric improvements six months after treatment show no significant differences when comparing TURP, contact laser prostatectomy and Vaportrode in men with LUTS suggestive of BPH.

References

1. Holtgrewe, H.L.: Current trends in management of men with lower urinary tract symptoms and benign prostatic hyperplasia. Urol., suppl. 4A, 51: 1, 1998.

2. Mebust, W.K., Holtgrewe, H.L., Cockett, A.T., Peters, P.C. and Writing Committee: Transurethral prostatectomy: immediate and post-operative complications. A cooperative study of 13 participating institutions evaluating 3885 patients. J. Urol., 141: 243, 1989.

3. Doll, H.A., Black, N.A., McPherson, K., Flood, A.B., Williams, B. and Smith, J.C. : Mortality, morbidity and complications following transurethral resection of the prostate for benign prostatic hypertrophy. J. Urol., 147: 1566, 1992.

4. Costello, A.J., Johnson, D.E. and Bolton, D.M.: Nd:YAG laser ablation of the prostate as a treatment for benign prostatic hypertrophy. Lasers Surg. Med., 12: 121, 1992.

5. Horninger, W., Janetschek, G., Watson, G., Reissigl, A., Strasser, H. and Bartsch, G.: Are contact laser, interstitial laser, and transurethral ultrasound-guided laser-induced prostatectomy superior to transurethral prostatectomy? Prostate, 31: 255, 1997.

6. Bush, I.M., Malters, E. and Bush, J.: Transurethral vaporization of the prostate (TVP): new horizons. Soc. Min. Invas. Ther., Suppl. 21: abstract, 1993.

7. Bosch, J.L.: Urodynamic effects of various treatment modalities for benign prostatic hyperplasia. J Urol., 158: 2034, 1997 .

8. Barry, M.J., Fowler jr., F.J., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L, Mebust, W.K., et al : The American Urological Association symptom index for benign prostatic hyperplasia. J. Urol., 148: 1549, 1992

9. Barry, M.J., Fowler jr., F.J., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L. and Mebust, W.K.: Measuring disease-specific health status in men with benign prostatic hyperplasia. Med. Care, suppl., 33: AS145, 1995.

10. Chatelain, C., Denis, L., Foo, K.T., Khoury, S., McConnell, J., Abrams, P., et al: Recommendations of the international scientific committee: Evaluation and treatment of lower urinary tract symptoms (LUTS) in older men. In: Benign Prostatic Hyperplasia, 5th International Consultation on BPH. edition 2001, Plymouth, UK, Plymbridge Distributors, pp. 519-534, 2001.

11. Schäfer, W.: Analysis of bladder-outlet function with the linearized passive urethral resistance relation, linPURR, and a disease-specific approach for grading obstruction: from complex to simple. World J. Urol., 13: 47, 1995.

12. Griffiths, D.J., van Mastrigt, R. and Bosch, J.L.: Quantification of urethral resistance and bladder function during voiding, with special reference to the effects of prostate size reduction on urethral obstruction due to benign prostatic hyperplasia. Neurourol. Urodyn., 8: 17, 1989.

13. van Venrooij, G.E., Boon, T.A. and de Gier, R.P.: International prostate symptom score and quality of life assessment versus urodynamic parameters in men with benign prostatic hyperplasia. J. Urol., 153: 1516, 1995.

14. Holtgrewe, H.L.: Guidance for clinical investigation of devices used for the treatment of benign prostatic hyperplasia. J. Urol., 150: 1588, 1993.

15. Roehrborn, C.G., Abbou, C-C., Akaza, H., Allona-Almagra, A., Boccon-Gibod, L., Ekman, P.E., et al: Clinical research criteria for studies of lower urinary tract symptoms (LUTS), enlarged prostate gland (EPG), bladder outlet obstruction (BOO) and benign prostatic hyperplasia (BPH). In: Benign Prostatic Hyperplasia, 5th International Consultation on BPH. Edited by C. Chatelain, L. Denis, K.T. Foo, et al edition 2001, Plymouth, UK, Plymbridge Distributors, pp. 319-396, 2001.

16. van Swol, C.F., van Vliet, R.J., Verdaasdonk, R.M. and Boon, T.A.: Electrovaporization as a treatment modality for transurethral resection of the prostate. Urol., 53: 317,1999.

17. Patel, A., Fuchs, G.J., Gutierrez-Acéves, J. and Andrade-Peréz, F.: Transurethral Electrovaporization and vapor-resection of the prostate: an appraisal of possible electrosurgical alternatives to regular loop resection. Br. J. Urol., 85: 202, 2000

18. Hammadeh, M.Y., Madaan, S., Singh, M. and Philip, T. : A 3-year follow-up of a prospective randomized trial comparing transurethral electrovaporization of the prostate with standard transurethral prostatectomy. Br. J. Urol., 86: 648, 2000.

19. Keoghane, S.R., Lawrence, K.C., Gray, A.M., Doll, H.A., Hancock, A.M., Turner, K. et al: A double-blind randomized controlled trial and economic evaluation of transurethral resection vs contact laser vaporization for benign prostatic enlargement: a 3-year follow-up. Br. J. Urol., 85: 74, 2000.

20. Tukhanen, K., Heino, A. and Ala-Opas, M.: Contact laser prostatectomy compared to TURP in prostatic hyperplasia smaller than 40 ml. Sic month follow-up with complex urodynamic assessment. Scand. J. Urol. Nephrol, 33: 31, 1999.

CHAPTER 5

A randomized controlled trial comparing transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia: analysis of subjective changes, morbidity and mortality

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Abstract

Purpose: We analyze subjective changes, morbidity and mortality in men with lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH) after transurethral resection of the prostate, contact laser prostatectomy and electrovaporization.

Materials and Methods: A prospective, randomized controlled trial was conducted on men with lower urinary tract symptoms, who met the criteria of the International Scientific Committee on BPH, had a prostate volume between 20 and 65 ml., and had Schäfer's obstruction grade 2 or greater. Objective morbidity was recorded for up to 12 months. Subjective morbidity was measured by a questionnaire completed by patients. Subjective changes were quantified using the International Prostate Symptom Score, Symptom Problem Index, Quality of Life question and BPH Impact Index. These indexes and the morbidity questionnaire were measured weekly for the first 6 weeks postoperatively and then at 3, 6 and 12 months.

Results: Transurethral prostatic resection was analyzed in 50 men, laser treatment in 45 and electrovaporization in 46. Baseline characteristics, and changes in the symptom scores up to 12 months postoperatively were similar. Perioperative blood loss and perforation were greatest in the resection group, and retention was greatest in the laser group. During the first 6 postoperative weeks there was less pain and less haematuria after resection, and less incontinence after laser prostatectomy.

Conclusions: Subjective changes are similar for transurethral prostatic resection, contact laser and electrovaporization. In the first 6 weeks after treatment there are only slight differences in pain, haematuria and incontinence among the therapies.

Introduction

Transurethral resection of the prostate is the most common surgical intervention for men with lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH). The last decade there has been an increasing number of men treated with pharmacotherapy, especially α-1 adrenergic blockers. However, not all patients can benefit from medication and require surgery[1]. Transurethral prostatic resection has been the gold standard for many decades but is associated with a mortality of 0% to 0.8% within 1 month postoperatively, and 2.8% within 1 year[2-5]. Intraoperative morbidity varies from 6.9% to 14% [2-5], especially bleeding and perforation. Morbidity within 30 days postoperatively varies from 9.5% to 18%, [2-5] and consists mainly of bleeding with or without clot retention, which can result in reoperation or transfusion. Late morbidity mainly consists of urethral strictures and bladder neck contractures, and is reported in up to11.2% of patients within 12 months[2].

In response to these complications a variety of alternative treatment modalities have been developed in the last decade. They all attempt to match the effects of transurethral prostatic resection but with lower mortality and morbidity. Contact laser prostatectomy and electrovaporization are 2 of these modalities which have shown good results in the past[6, 7].

We performed a randomized controlled trial in which we compared contact laser prostatectomy and electrovaporization with the gold standard transurethral prostatic resection. Previously we analyzed the urodynamic effects of these 3 treatment modalities[8]. There were obvious significant changes in maximum flow, cystometric capacity and obstruction grade, as well as other relevant changes, all of which were not significant, among the 3 treatment groups.

The main reasons patients seek help for BPH are symptom bothersomeness and negative impact of lower urinary tract symptoms on quality of life[9]. The International Consensus Committee on BPH emphasized that therapy must be initiated according to the degree of symptom bothersomeness[10]. The Measurement Committee of the American Urological Association has developed and validated several questionnaires to quantify subjective parameters of symptoms, bothersomeness of symptoms, quality of life and impact of urinary problems on various domains of health[11-12].

We analyze and compare subjective changes, morbidity and mortality following transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with lower urinary tract symptoms associated with BPH.

Materials and Methods

This prospective, randomized controlled study was performed between 1996 and 2001 at our medical center. The study included 141 men older than 45 years of age with lower urinary tract symptoms associated with BPH. History was taken in all patients, and digital rectal examination, transrectal ultrasonography, urodynamic evaluation, free flowmetry, post-void residual volume estimation, urinalysis and blood analysis were performed. Perioperative parameters of operative time, irrigation fluid volume, amount of blood loss, duration of bladder drainage and complications up to 12 months postoperatively were recorded.

The International Prostate Symptom Score (I-PSS)[11], Quality of Life (QoL)[11] , Symptom Problem Index (SPI or Bother Score)[12] and BPH Impact Index (BII)[12] were completed preoperatively, and 1 week, 6 weeks, 3 months, 6 months and 12 months postoperatively. Specific morbidity and symptomatic aspects were studied using a self-developed questionnaire that was completed by patients once preoperatively, and at weekly intervals during the first 6 weeks and 3, 6 and 12 months postoperatively. Questions concerned pain in the lower abdominogenital region, pain during voiding, haematuria, incontinence, urge and hesitancy. Patients indicated how many days they had 1 of these symptoms in the last week (score 0 to 7) and its severity (1 only minor symptoms to 5 severe symptoms). Together with the morbidity questionnaire, patients were asked to report the average number of voids during the daytime and nighttime for the last week.

Inclusion criteria were prostate volume between 20 and 65 ml. and a Schäfer obstruction grade 2 or greater. Exclusion criteria were those of the International Consensus Committee on BPH[10].

Patients were randomized using opaque envelopes. Transurethral prostatic resection was performed with a standard 24Fr resectoscope using glycine for irrigation.

Laser prostatectomy was performed using an SLT Nd:YAG laser (Surgical Laser Technologies, Oaks, Pennsylvania) with an MTRL 10, 6 x 5 mm sapphire tipped probe. A Morgenstern scope was used to introduce the glass fiber with the contact probe. Isotonic salt solution was used as irrigation fluid. Electrovaporization was performed with a Vaportrode (Circon-Acmi, Stanford, Connecticut) element using glycine for irrigation.

Patients randomized for resection or electrovaporization were operated on alternately by experienced urologists and trainees. Patients for contact laser were mostly operated on by 1 experienced urologist together with a trainee. All patients received intravenous antibiotics intraoperatively. If necessary, a suprapubic catheter was inserted intraoperatively. Postoperatively a 20Fr transurethral catheter was left indwelling.

Group size was calculated with 90% power and a 5% 2-tailed significance level as described in detail previously[8], which resulted in a group size of 32 men. This number agrees with the minimum number of 30 men recommended by the American Urological Association New Technology Assessment Committee[13].
The Kolmogorov-Smirnov goodness-of-fit test was used to examine whether a variable was distributed normally. A number of parameters are reported as mean with standard deviation (SD). Further statistical analyses were done with Fisher's Exact test, Pearson chi-square test, 1-way-ANOVA, Kruskal-Wallis nonparametric test, Student's t test, Mann-Whitney *U* test and Wilcoxon test.

Results

The baseline characteristics of the remaining 141 included patients are listed in table 1. Except for the effective capacity, no statistically significant differences between the three treatment groups were detected.
Table 2 shows the perioperative data. Mean operation time was within one hour and did not differ significantly between the three groups (p=0.09). Intra-operative visually estimated blood loss was significantly lower in the laser and electrovaporization group compared to the transurethral prostatic resection group (p<0.001). A significant decrease of haemoglobin concentrations (mmol/l) was only seen within the transurethral prostatic resection group. This decrease was significantly (p<0.001) more in the transurethral prostatic resection group compared to the other groups. The use of irrigation fluid was lowest in the electrovaporization group and this was significantly lower than in the laser group (p=0.01). Drainage time and hospital stay did not differ significantly among the groups.
Table 3 shows the intraoperative complications. Contact laser often caused tissue debris, which sometimes made conversion to transurethral prostatic resection necessary. Transurethral prostatic resection had the highest risk of capsule perforations. Table 4 shows the postoperative morbidity and mortality up to twelve months postoperatively.
The prevalence of urinary tract infections, confirmed by culture, were for transurethral prostatic resection, contact laser and electrovaporization 10%, 9% and 5% one week postoperatively and 10%, 8% and 10% after six weeks respectively.
Table 5 lists the subjective AUA scores for the different treatment groups preoperatively and 12 months postoperatively together with the change. Figure 1a-d shows graphic representations of these scores during all six intervals. In all treatment groups there were obvious and significant differences between the pre-operative scores and the 12 month postoperative scores (p<0.001). For the symptom score index (I-PSS) and symptom problem index (SPI) there were no significant differences among the different treatment groups 12 months

Table 1 Mean ± standard deviation of baseline characteristics of the 3 treatment groups.

	TURP	Contact Laser	Vaportrode
Number of patients analyzed	50	45	46
Mean age (years)	66 ± 8	67 ± 9	64 ± 10
Prostate Volume (ml)	37 ± 11	37 ± 11	35 ± 11
Maximum Free Flow (ml/s)	11 ± 4	12 ± 4	11 ± 4
Schäfer Obstruction Grade	3 ± 1	3 ± 1	3 ± 1
Effective Capacity [1] (ml)	350 ± 140	300 ± 135	290 ± 145
Symptom Score Index	16.8 ± 6.0	18.9 ± 6.8	20.2 ± 6.6
Symptom Problem Index (Bother Score)	11.9 ± 6.7	12.5 ± 7.8	14.1 ± 6.7
Quality of Life	3.8 ± 1.5	3.7 ± 1.6	4.1 ± 1.4
BPH Impact Index	9.6 ± 4.7	9.3 ± 4.2	10.8 ± 4.1

1. Effective capacity = maximum cystometric capacity – post void residual volume.

Table 2 Mean ± standard deviation of perioperative parameters.

	TURP	Contact Laser	Vaportrode
Operation time (min)	58 ± 26 range: 25 - 150	58 ± 11 range: 30 - 80	50 ± 16 range: 20 - 90
Blood loss intraoperatively [1]	1.1 ± 0.3	0.6 ± 0.7	0.6 ± 0.6
Change in Hb (mmol/l) [2]	9.2 → 8.4 p < 0.001	9.0 → 8.8 p = 0.3	8.8 → 8.6 p = 0.07
SPC intraoperatively [3]	49% and 2%	9% and 6%	27% and 5%
Irrigation fluid (l)	16 ± 7	18 ± 4	14 ± 8
Drainage time (days)	2.1 ± 0.7	2.8 ± 3.1	1.9 ± 0.6
Postoperative hospital stay (days). Mean ± SD	3.9 ± 0.9	3.8 ± 1.3	3.4 ± 0.9
Postoperative hospital stay (days). Median with 2.5 and 97.5 percentiles	4.0 (3.0-5.9)	3.5 (2.0-6.0)	3.0 (2.0-5.0)

1. Blood loss: 0=none, 1=moderate and 2=severe. Visual estimation intraoperatively by urologist.
2. Hb = haemoglobin: pre → postoperative value, including significance of decrease within group.
3. SPC = suprapubic catheter. Percentage of patients receiving an SPC intraoperatively and percent of patients who received an SPC already preoperatively because of micturition problems.

Table 3 Number of intraoperative complications (all operations included, also when patients were excluded for further analysis).

	TURP	Contact laser	Vaportrode
Capsule perforation	5	2	2
Bleeding, making electro-coagulation necessary	-	2	1
Bleeding, making TURP necessary	-	3	0
Fausse route	1	1 [1]	0
Technical failure	0	3	2
Conversion to TURP because of tissue debris	-	3	1
Urethral injury	1	0	0

1. Fausse route made during first introduction of the scope.

Table 4 postoperative morbidity and mortality within 12 months (without urinary tract infections)

	TURP	Contact Laser	Vaportrode
Bleeding requiring transfusion	1	0	0
Clot retention	1	2	0
Urinary retention	0	5	0
Re-operation (TURP)	2	1	2
Strictures	1 meatus 2 urethral	2 urethral	1 urethral
Other	1 myocardial infarction	1 epididymitis	1 penile deviation
Mortality	1 cardiac failure 1 hepatic failure	0	0

Table 5 Mean ± standard deviation of subjective scores from AUA questionnaires of the 3 treatment groups

	Pretreatment	12 months Posttreatment	Change as ratio and percent [a]
Symptom Score Index			
TURP	16.8 ± 6.0	4.6 ± 4.8	0.27 (-73%)
Laser	18.9 ± 6.8	5.8 ± 5.7	0.31 (-69%)
Vaportrode	20.2 ± 6.6	6.7 ± 6.4	0.33 (-67%)
Symptom Problem Index (Bother Score)			
TURP	11.9 ± 6.7	2.4 ± 4.7	0.20 (-80%)
Laser	12.5 ± 7.8	2.4 ± 3.3	0.19 (-81%)
Vaportrode	14.1 ± 6.7	4.2 ± 5.2	0.29 (-71%)
Quality of Life			
TURP	3.8 ± 1.5	0.9 ± 1.2	0.23 (-77%)
Laser	3.7 ± 1.6	1.0 ± 0.9	0.26 (-74%)
Vaportrode	4.1 ± 1.4	1.4 ± 1.4	0.35 (-65%)
BPH Impact Index			
TURP	9.6 ± 4.7	2.4 ± 3.8	0.25 (-75%)
Laser	9.3 ± 4.2	2.0 ± 2.2	0.22 (-78%)
Vaportrode	10.8 ± 4.1	3.8 ± 4.1	0.35 (-65%)

1. Ratio = post value/ pre value, and percentual change = {(pre value – post value)/ pre value} * 100%

postoperatively, nor at any other time interval. For the quality of life (QoL) there was a significant difference (p=0.03) one week postoperatively, in favour of the group treated with contact laser. QoL changed one week postoperatively from 3.8 to 4.0 in the transurethral prostatic resection group, from 4.1 to 3.8 in the electrovaporization group and from 3.7 to 2.4 in the laser group. At six weeks postoperatively there was no significant difference among the three treatment modalities anymore, nor at any other time interval. For the BPH impact index (BII) there were no significant differences among the three treatment modalities at any interval, although there was a trend suggesting a larger decrease in BII for patients treated with the contact laser.

Figure 2a shows a graphic representation of daytime frequency. There was a significant (p<0.02 in all groups) decrease from about 8.5 to about 6.5. There were no significant differences between the groups at any time interval. There was a slight increase of frequency during the first weeks postoperatively in all groups. After about six weeks the number of voids during daytime returned to the pre-operative value, after which it dropped further.

Figure 2b shows a graphical representation of nocturia. There was a significant ($p \leq 0.01$ in all groups) decrease from about 2.5 to 1.5. There were no significant differences between the groups at all time intervals. There was a slight increase during the first 2 weeks for all groups. At 3 months postoperatively nocturia was significant lower than preoperatively in all groups ($p<0.001$).
Figures 3-8 show graphic representations of morbidity and symptomatic parameters. Figures 3a-8a show the percentage of patients having a symptom in the last week. Figures 3b-8b show the average severity of a symptom (score 1-only minor symptoms to 5-severe symptoms) multiplied by the number of days (0 to 7) a symptom was present during the last week calculated from the data of all patients. The duration-severity data were statistically analyzed. There were no significant differences in baseline values for all parameters between the groups. Postoperatively there were also no significant differences between the treatment groups at any time interval, except for haematuria. There is an obvious trend for a lower incidence and duration-severity product for haematuria in patients treated with transurethral prostatic resection. Only at 4 weeks postoperatively this is statistically significant ($p=0.01$). There is a not significant trend showing less pain during voiding and abdomino-genital pain postoperatively in the transurethral prostatic resection group. In the laser group there is a trend suggesting less incontinence postoperatively.

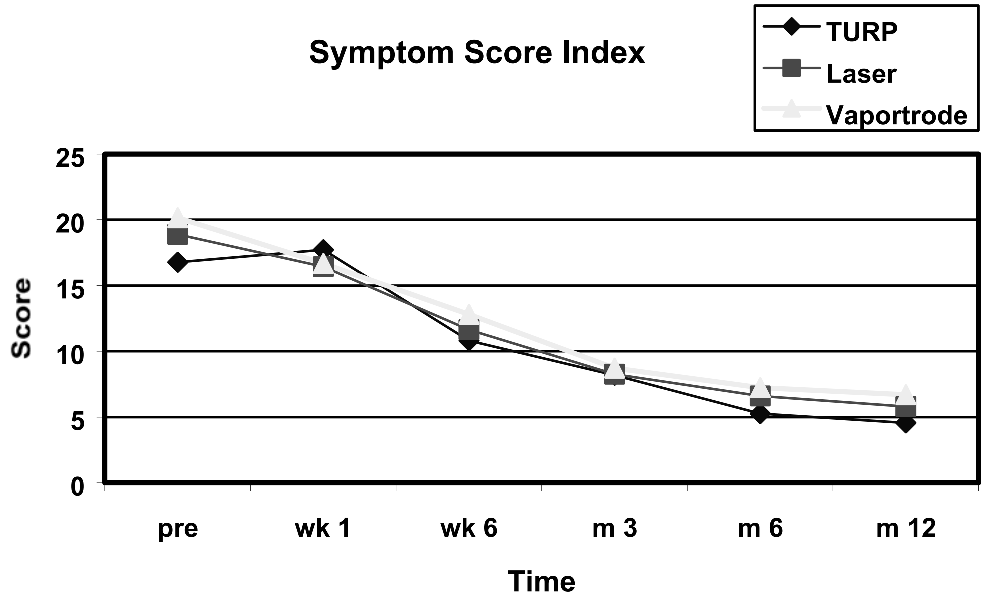


Figure 1a Average symptom score index preoperatively and postoperatively up to 12 months after transurethral resection of the prostate (TURP), contact laser prostatectomy (Laser) and electrovaporization (Vaportrode).

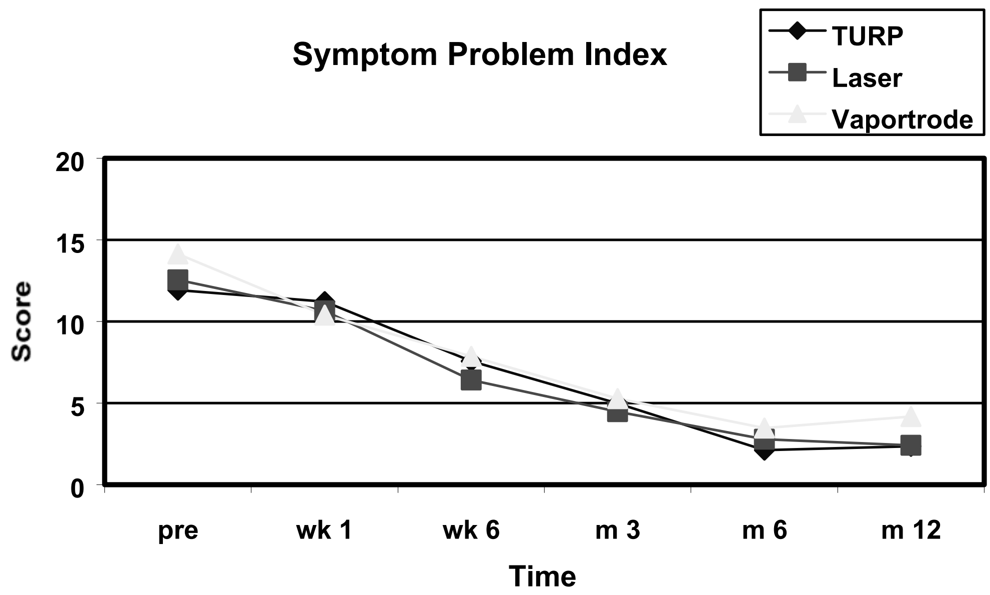


Figure 1b Average symptom problem index preoperatively and postoperatively up to 12 months after transurethral resection of the prostate (TURP), contact laser prostatectomy (Laser) and electrovaporization (Vaportrode).

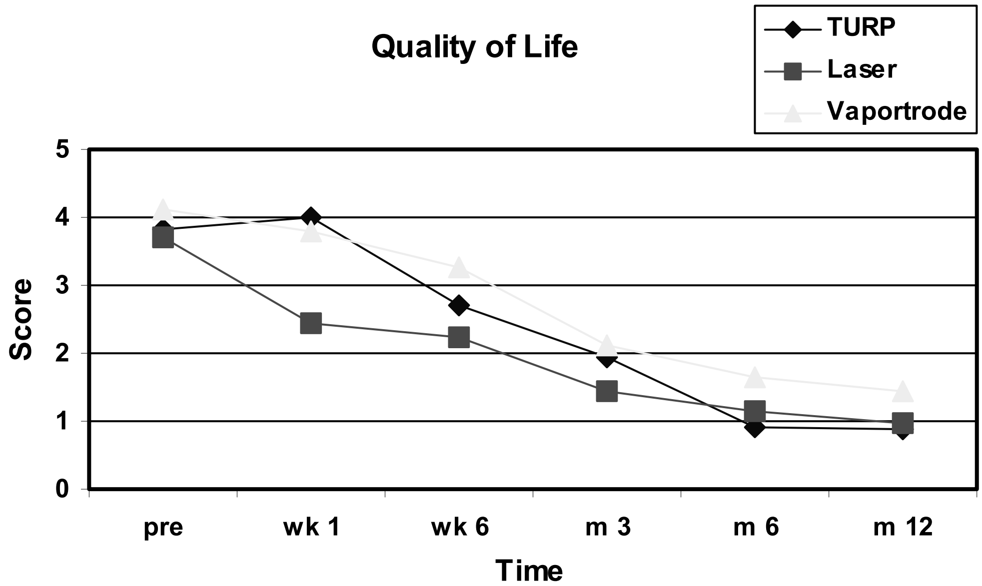


Figure 1c Average quality of life score preoperatively and postoperatively up to 12 months after transurethral resection of the prostate (TURP), contact laser prostatectomy (Laser) and electrovaporization (Vaportrode).

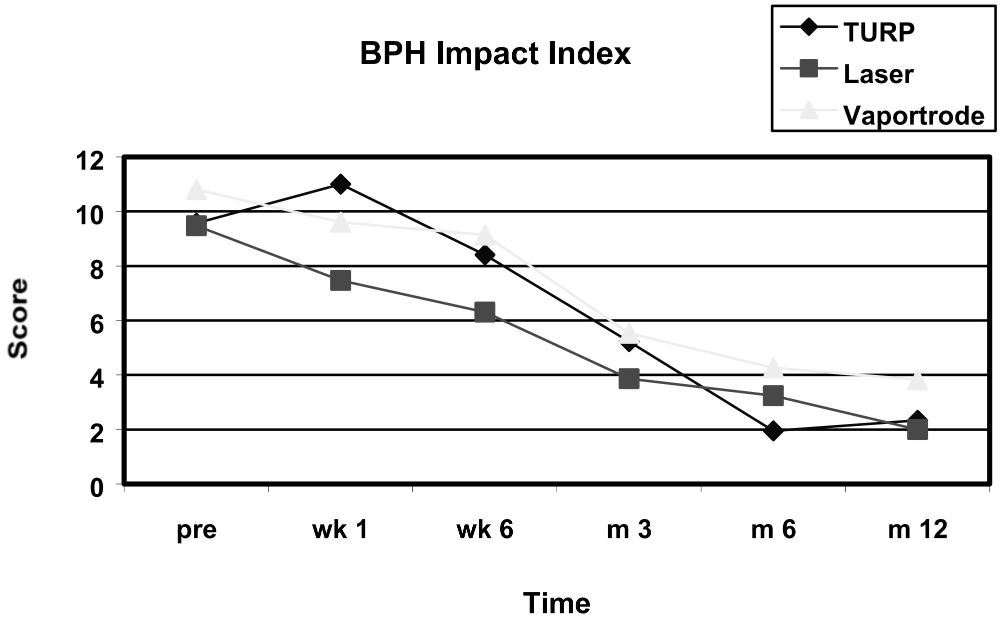


Figure 1d Average BPH impact index preoperatively and postoperatively up to 12 months after transurethral resection of the prostate (TURP), contact laser prostatectomy (Laser) and electrovaporization (Vaportrode).

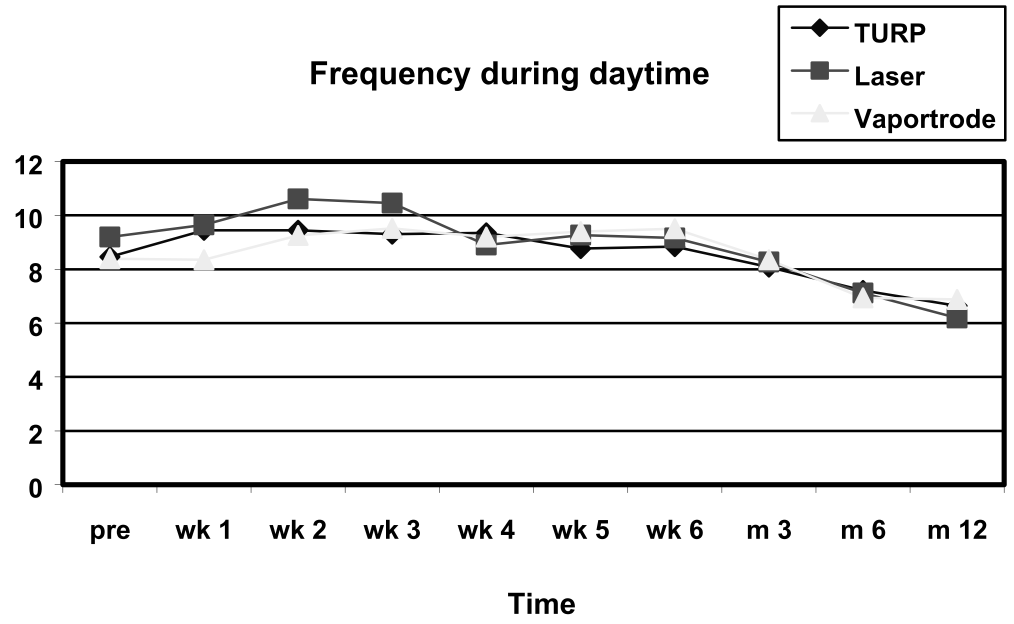


Figure 2a Number of daytime voids (frequency during daytime) preoperatively and postoperatively up to twelve months after transurethral resection of the prostate (TURP), contact laser prostatectomy (Laser) and electrovaporization (Vaportrode).

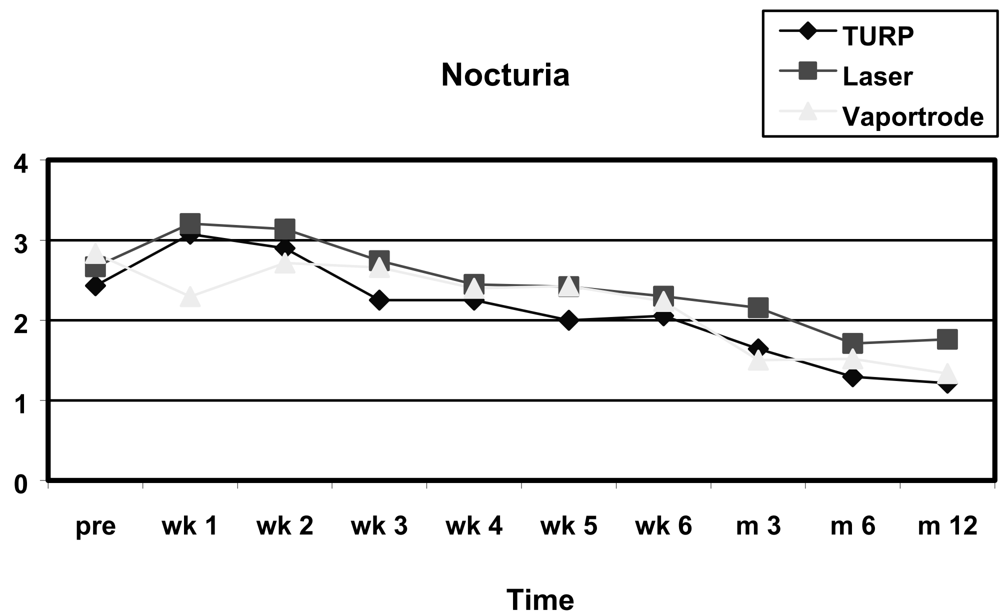
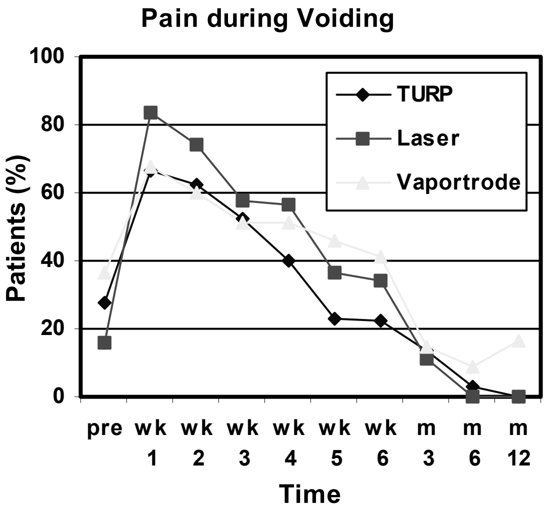
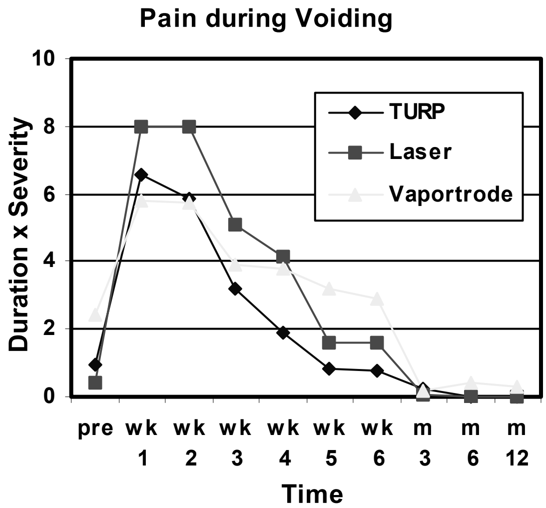
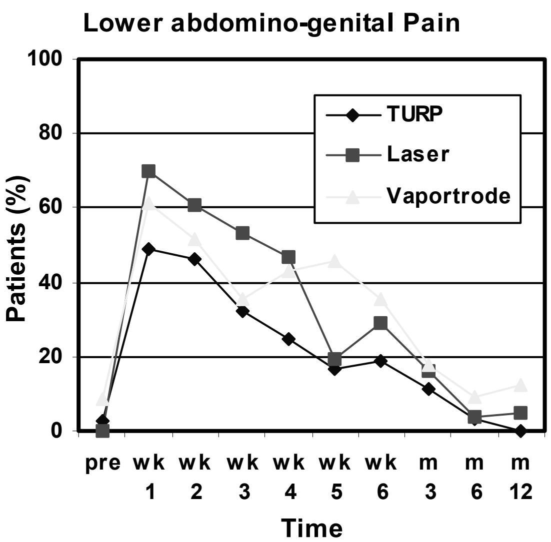


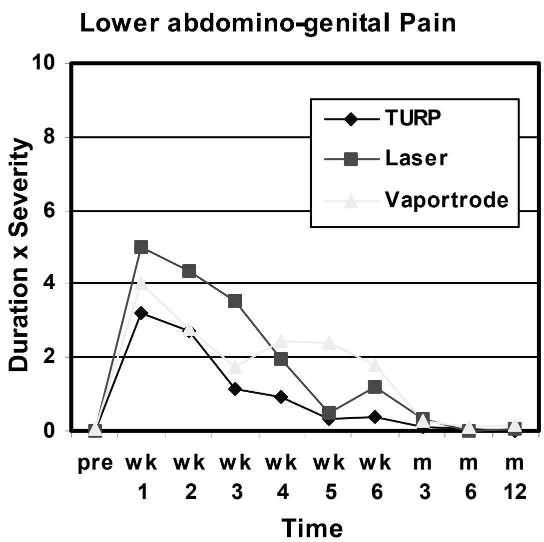
Figure 2b Number of nighttime voids (nocturia) preoperatively and postoperatively up to twelve months after transurethral resection of the prostate (TURP), contact laser prostatectomy (Laser) and electrovaporization (Vaportrode).



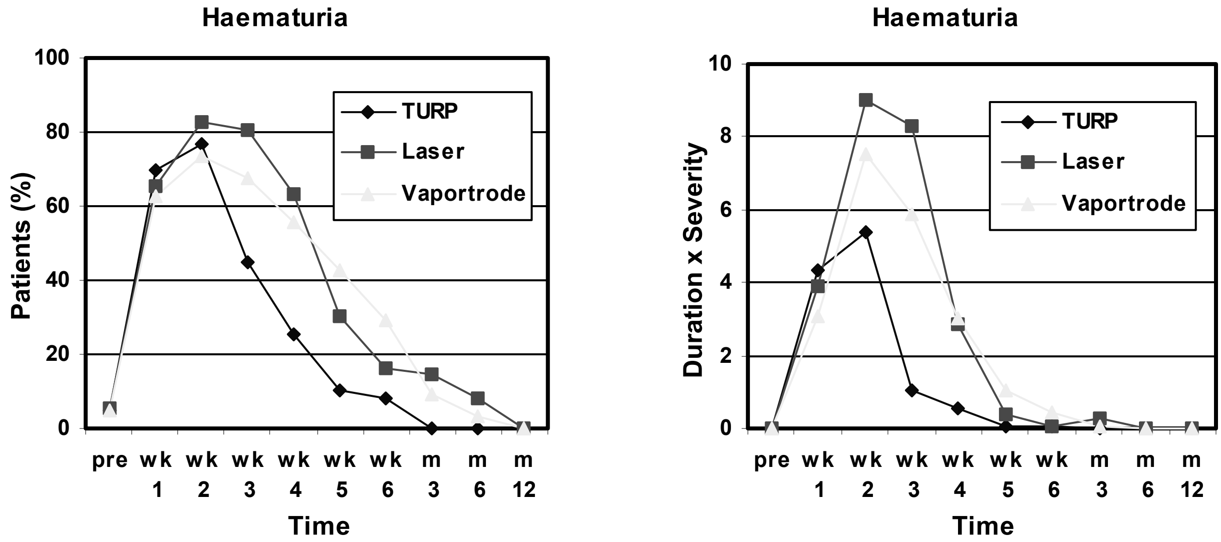


Figures 3a and 3b Percentage of patients with pain during voiding in the last week (a) and average severity (score 1 to 5) times number of days (0 to 7) pain during voiding was present in the last week (b).

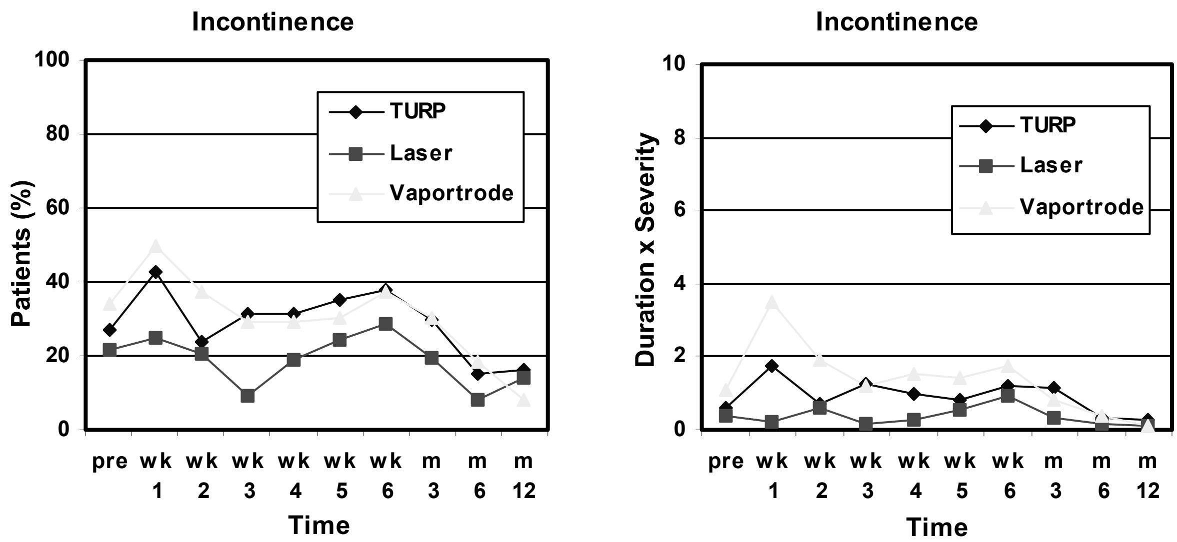




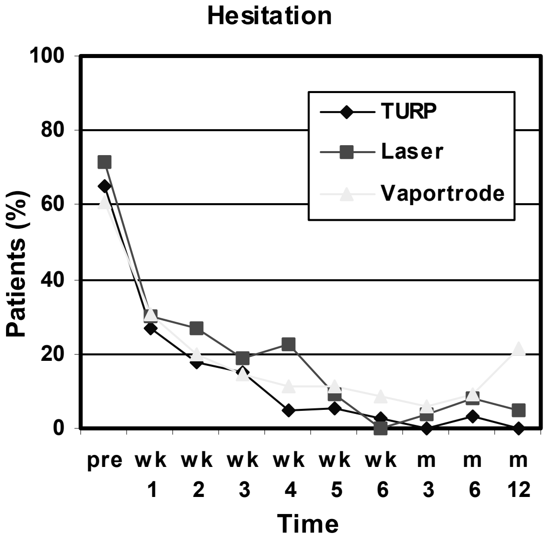
Figures 4a and 4b Percentage of patients with lower abdomino-genital pain in the last week (a) and average severity (score 1 to 5) times number of days (0 to 7) lower abdomino-genital pain was present in the last week (b).

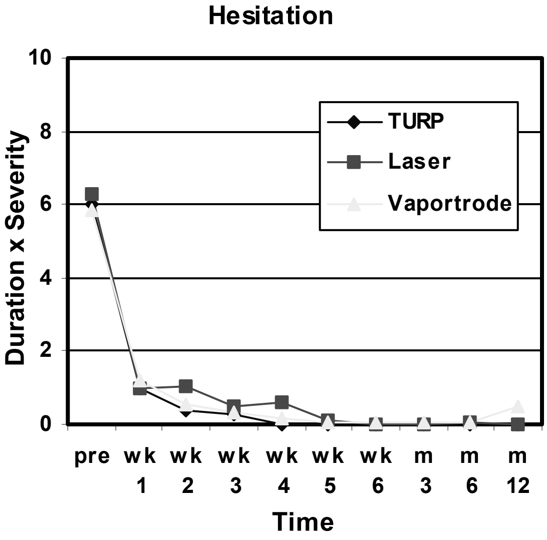


Figures 5a and 5b Percentage of patients with haematuria in the last week (a) and average severity (score 1 to 5) times number of days (0 to 7) haematuria was present in the last week (b).

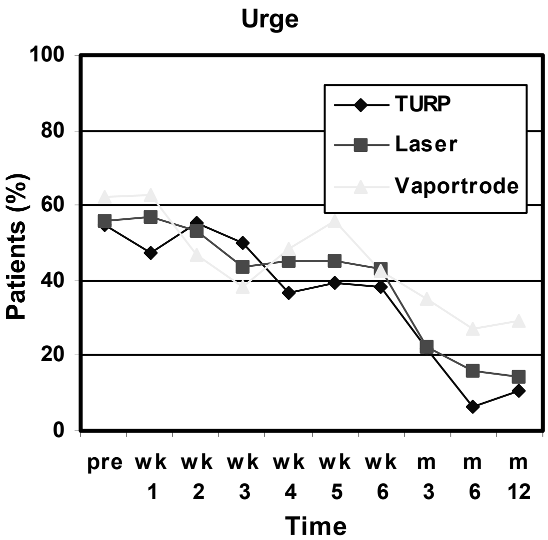


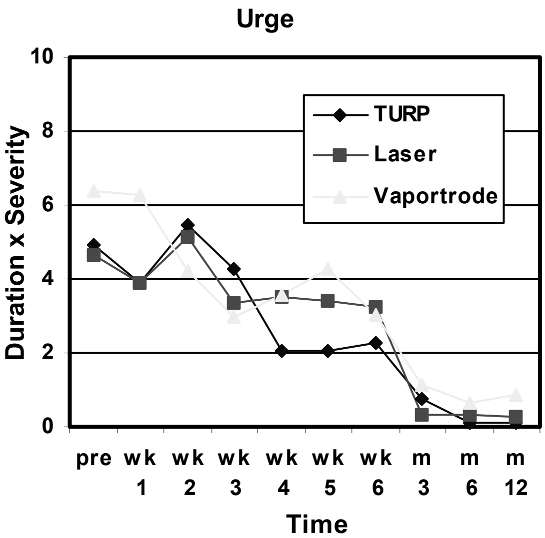
Figures 6a and 6b Percentage of patients with incontinence in the last week (a) and average severity (score 1 to 5) times number of days (0 to 7) incontinence was present in the last week (b).





Figures 7a and 7b Percentage of patients with hesitation in the last week (a) and average severity (score 1 to 5) times number of days (0 to 7) hesitation was present in the last week (b).





Figures 8a and 8b Percentage of patients with urge in the last week (a) and average severity (score 1 to 5) times number of days (0 to 7) urge was present in the last week (b).

Discussion

A previous article about this study group demonstrated that these three treatment modalities score urodynamically equally six months postoperatively[8]. Urodynamic changes are however not always related to subjective changes and the latter are nowadays concerned to be of high importance in treatment decision[9]. This study shows that there are no significant differences among the three treatments concerning symptom score index (I-PSS), symptom problem index (SPI) and BPH impact index (BII) at all time intervals up to twelve months. In the latter there was a trend in favour of contact laser. Quality of life (QoL) improved (the score decreased) significantly faster in the laser group, although after six weeks the values were very similar again. This might be of some clinical importance. The changes in I-PSS are similar to those reported in other studies which compared contact laser with transurethral prostatic resection[6, 14, 15] and which analyzed electrovaporization[16, 17]. Unfortunately, most studies only evaluated I-PSS and few also other AUA scores.

Number of voids during daytime and nocturia decreased significantly for all groups and without significant differences between them. Nocturia is a symptom that causes much bothersomeness[9] and frequency is strongly associated with well-being[9].

Morbidity and mortality in patients undergoing transurethral prostatic resection have been analyzed in several large, mostly retrospective, studies[2-5]. These studies demonstrate a decrease in mortality rate over the last decades, but an almost unchanged morbidity rate. Morbidity is a parameter which is not strictly defined: haematuria is a complication for most urologists if it requires blood transfusion, re-operation or leads to clot retention. In the patient's view haematuria with painful clots during voiding can be regarded as morbidity. Doll[5] discusses shortly this problem, which is one of the complicating factors in comparing literature. Morbidity and mortality in our transurethral prostatic resection group is comparable to these large scale, retrospective studies. Keoghane[14] compared prospectively the same contact laser with transurethral prostatic resection. They quantified peri-operative blood loss and this ranged in the laser group from 0 – 200ml (median 39ml) and in the transurethral prostatic resection group from 12 – 1600ml (median 200ml). Change in haemoglobin concentration was also statistically different in favour of laser. Four of their 72 laser patients were converted to transurethral prostatic resection because of bleeding, which agrees with our three conversions out of 58 men. Postoperatively none of their laser patients required blood transfusion, whereas 20% of patients undergoing transurethral prostatic resection were transfused. In our study we required only one blood transfusion in the transurethral prostatic resection group. Hospital stay was comparable to our results and duration of catheterization was shorter in their study group. Tukhanen[15] compared prospectively contact laser and transurethral prostatic resection and demonstrated a significant difference in

estimated blood loss being 0-220ml in the contact laser group (mean 57ml) and 30-520ml in the transurethral prostatic resection group (mean 175ml). Hospital stay is comparable to our study. They only treated prostates with a volume smaller than 40 ml and this probably explains their reported low incidence of intra- and post-operative complications.
Hammadeh[16] showed significant less decrease of haemoglobin during electrovaporization in a randomized trial comparing electrovaporization and transurethral prostatic resection. No blood transfusions were required. Post-operative complications are comparable to ours. Matos-Ferreira[17] analyzed electrovaporization and showed comparable results with negligible blood loss and no blood transfusions. Mean drainage time was 24 h and re-catheterization was necessary in 5.5%. There were minimal post-operative complaints and one urethral stricture, but follow-up time is not mentioned.

Summarized, previously[8] it was demonstrated that after six months there are no urodynamic differences between the three treatment modalities. The present study demonstrates that there is a comparable subjective improvement over twelve months postoperatively. Intra-operatively there is significantly more blood loss and there are more capsule perforations in the transurethral prostatic resection group. Postoperatively there is a comparable morbidity, although several parameters cannot be compared statistically. transurethral prostatic resection shows less post-operative pain and haematuria and contact laser shows less incontinence. Paradoxically, transurethral prostatic resection patients show most intra-operative blood loss, but lowest post-operative haematuria. Post-operative urinary retention is highest in the laser group. Comparing contact laser and electrovaporization there is often (also urodynamically) a trend in favour of contact laser. The latter seems to be a good alternative for transurethral prostatic resection. Contact laser might even have a larger therapeutic range, because it offers surgical options for patients on anticoagulant therapy or bleeding disorders[18,19] . transurethral prostatic resection is often contraindicated for these patients. There is however the opinion that large prostates (arbitrarily larger than 40 ml)[15] are more difficult to treat. Optical results intra-operatively in contact laser prostatectomy are sometimes less spectacular compared to transurethral prostatic resection, but post-operative analysis demonstrates few differences. Long-term follow-up however is mandatory and is in progress at this moment.

Conclusions

When comparing transurethral prostatic resection, contact laser prostatectomy and electrovaporization in men with lower urinary tract symptoms associated with BPH, there is an almost similar course in change in subjective scores, like symptom score index, symptom problem index, quality of life and BPH impact index up to twelve months postoperatively. Intra-operatively there is more blood loss and there are more capsule perforations in patients undergoing transurethral prostatic resection. Postoperatively urinary retention is highest in the laser group. Further there is less pain and haematuria in patients after transurethral prostatic resection during the first 6 weeks. In the same time period there is less incontinence after contact laser.

Acknowledgement

We are grateful for statistical advice from dr. Paul Westers from the department of biostatistics in Utrecht.

References

1. Holtgrewe, H.L.: Current trends in management of men with lower urinary tract symptoms and benign prostatic hyperplasia. Urol., suppl. 4A, 51: 1, 1998.

2. Horninger, W., Unterlechner, H., Strasser, H. and Bartsch, G.: Transurethral prostatectomy: mortality and morbidity. Prostate 28: 195, 1996.

3. Mebust, W.K., Holtgrewe, H.L., Cockett, A.T., Peters, P.C. and Writing Committee: Transurethral prostatectomy: immediate and post-operative complications. A cooperative study of 13 participating institutions evaluating 3885 patients. J. Urol., 141: 243, 1989.

4. Uchida, T., Ohori, M., Soh, S., Sato, T., Iwamura, M., Oa, T. et al: Factors influencing morbidity in patients undergoing transurethral resection of the prostate. Urol., 53: 98, 1999

5. Doll, H.A., Black, N.A., McPherson, K., Flood, A.B., Williams, G.B. and Smith, J.C.: Mortality, morbidity and complications following transurethral resection of the prostate for benign prostatic hypertrophy. J. Urol., 147: 1566, 1992.

6. Horning, W., Janetschek, G., Watson, G., Reissigl, A., Strasser, H. and Bartsch, G.: Are contact laser, interstitial laser, and transurethral ultrasound-guided laser-induced prostatectomy superior to transurethral prostatectomy? Prostate, 31: 255, 1997.

7. Patel, A., Fuchs, G.J., Gutierrez-Acéves, J. and Andrade-Peréz, F.: Transurethral electrovaporization and vapor-resection of the prostate: an appraisal of possible electrosurgical alternatives to regular loop resection. Brit. J. Urol., 85: 202, 2000.

8. Van Melick, H.H., van Venrooij, G.E., Eckhardt, M.D. and Boon, T.A.: A randomized controlled trial comparing transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia: urodynamic effects. J. Urol., 168: 1058, 2002.

9. Eckhardt, M.D., van Venrooij, G.E., van Melick, H.H. and Boon, T.A. : Prevalence and bothersomeness of lower urinary tract symptoms in benign prostatic hyperplasia and their impact on well-being. J. Urol., 166: 563, 2001.

10. Chatelain, C., Denis, L., Foo, K.T., Khoury, S., McConnell, J., Abrams, P. et al: Recommendations of the international scientific committee: Evaluation and treatment of lower urinary tract symptoms (lower urinary tract symptoms) in older men. In: Benign Prostatic Hyperplasia, Proceedings of the 5th International Consultation on BPH. edition 2001, Plymouth, UK, Plymbridge Distributors, pp. 519-534, 2001.

11. Barry, M.J., Fowler jr., F.J., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L., Mebust, W.K. et al: The American Urological Association symptom index for benign prostatic hyperplasia. J. Urol., 148: 1549, 1992.

12. Barry, M.J., Fowler jr., F.J., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L., Mebust, W.K. et al: Measuring disease-specific health status in men with benign prostatic hyperplasia. Med. Care, Suppl., 33: AS145, 1995.

13. Holtgrewe, H.L.: Guidance for clinical investigation of devices used for the treatment of benign prostatic hyperplasia. J. Urol., 150: 1588, 1993.

14. Keoghane, S.R., Lawrence, K.C., Gray, A.M., Doll, H.A., Hancock, A.M., Turner, K. et al: A double-blind randomized controlled trial and economic evaluation of transurethral resection vs contact laser vaporization for benign prostatic enlargement: a 3-year follow-up. Br. J. Urol., 85: 74, 2000.

15. Tukhanen, K., Heino, A. and Ala-Opas, M.: Contact laser prostatectomy compared to transurethral prostatic resection in prostatic hyperplasia smaller than 40 ml. Scand. J. Urol. Nephrol., 33: 31, 1999

16. Hammadeh, M.Y., Fowlis, G.A., Singh, M. and Philip, T.: Transurethral electrovaporization of the prostate - a possible alternative to transurethral resection: a one-year follow-up of a prospective randomized trial. Br. J. Urol., 81: 721, 1998.

17. Matos-Ferreira, A. and Varregoso, J.: Electrovaporization of the prostate in men with benign prostatic enlargement. Br. J. Urol., 80: 575, 1997

18. Mueller, E.J.: Contact laser vaporization of the prostate in patients on chronic anticoagulant therapy. Tech. Urol., 4: 156, 1998.

19. Keoghane, S.R. and Cranston, D.W.: Contact laser prostatectomy in anti-coagulated patients: mixed results. Br. J. Urol., 77: 613, 1996.

CHAPTER 6

Long-term follow-up after transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia

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Urology, accepted

Abstract

Objectives: To compare long-term results of subjective changes, flowmetry, morbidity and mortality after transurethral prostate resection (TURP), contact laser prostatectomy (CLP) and electrovaporization in men with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

Methods: A prospective randomized controlled trial was conducted. Included were men with LUTS, who met the criteria of the International Scientific Committee on BPH, had a prostate volume between 20 and 65 ml and a Schäfer's obstruction grade $\geq$2. Subjective changes were quantified using the International Prostate Symptom Score (I-PSS), Symptom Problem Index (SPI), Quality of Life (QoL) question and BPH Impact Index (BII). Morbidity was registered objectively and by patient questionnaires. Maximum flow was measured by free uroflowmetry. These parameters were measured at regular intervals up to one year. At the end of 2002, all patients were invited for a long-term follow-up including the aforementioned parameters.

Results: Fifty men were randomized for TURP, 45 for laser treatment and 46 for electrovaporization. Seventy percent could be followed up to maximally 7 years. Values for I-PSS, SPI, QoL score and BII increased slightly after a mean follow-up time of 4.3 years. Maximum uroflow decreased similarly in all treatment groups to about 150% of the values preoperatively. Morbidity, reoperation rates and mortality were also similar.

Conclusions: This up to seven years follow-up, demonstrates durable subjective and objective results for patients with LUTS associated with BPH after TURP, CLP or electrovaporization. There were no clinically relevant differences between these modalities.

Introduction

Today's Western world is facing an aging population with all its medical problems. For urologists this creates an enormous increase in men with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). One of the major challenges is to treat men who are bothered by these symptoms with a minimum of side effects and complications. Nowadays, most patients are treated with pharmacotherapeutics with less side effects, but also less efficacy than surgical treatment[1]. Therefore there is still a need for surgical intervention with transurethral resection of the prostate (TURP) as gold standard. However, TURP is associated with a rather high morbidity and mortality[2,3] . In the past 10-15 years, new technologies led to the introduction of a variety of surgical treatment modalities. However, TURP is still the gold standard, which might partially be explained by a lack of evidence for durable long-term results of these new treatments.
At our clinic, a randomized controlled study comparing TURP, contact laser prostatectomy and electrovaporization has been conducted in men with LUTS associated with BPH. In previous articles we published the urodynamic results six months postoperatively[4] and subjective and symptomatic changes at various time intervals up to twelve months[5], together with morbidity and mortality. Results were very similar between all treatment modalities.
To address the importance of demonstrating durability, we studied the subjective and objective results of a long-term follow-up.

Material and methods

This prospective randomized controlled study was carried out between 1996 and 2001 at our clinic. Included were men over 45 years of age with LUTS associated with BPH. All patients underwent history taking, digital rectal examination, transrectal ultrasonography, urodynamic evaluation, free flowmetry, post-void residual volume estimation, urinalysis and blood analysis.
Patients had to be urodynamically equivocal or obstructed (Schäfer grade ≥2). Their prostate volume had to be between 20 and 65 ml. Patients with any of the exclusion criteria of the International Consensus Committee on BPH were excluded from analysis[6].
Symptomatic and subjective changes were measured by questionnaires validated by the American Urological Association (AUA). Patients completed the International Prostate Symptom Score Index (IPSS)[7], the Symptom Problem Index (SPI)[8], the BPH Impact Index (BII)[8] and the Quality of Life question (QoL)[7].

Next to objective complications, some specific morbidity and symptomatic aspects were studied using a self-developed questionnaire that was completed by patients. All questionnaires were completed preoperatively and postoperatively at regular intervals including 6 and 12 months. The self-developed questionnaire concerned pain in the lower abdomino-genital region, pain during voiding, haematuria, incontinence, urge and hesitation. Patients had to indicate for how many days they had one of these symptoms in the last week (score 0 to 7). If a symptom was present, they had to indicate its severity (score 1-only minor severity to 5-high severity). Together with the morbidity questionnaire, patients were asked to report the average number of voids during daytime and nighttime for the last week.

Free uroflowmetry was performed at the same time intervals. Uroflowmetric results were only included if patients voided over 150 ml. Complications were registered both intraoperatively and postoperatively.

In fall 2002, all patients who were operated on for more than 18 months ago were re-invited to visit the outpatient department. This was primarily done by one or two letters and if necessary by phone in a last attempt. Patients who were previously excluded, were not invited. In this way, follow-up times varied individually from 1.5 to 7 years. The same questionnaires and tests were used as during the 12 months follow-up.

Details concerning TURP, laser prostatectomy and electrovaporization are described previously[5].

Group size was calculated with 90% power and a 5% two-tailed significance level as described in detail previously[4]. This resulted in a group size of 32 men. This number agrees with the minimum number of 30 men recommended by the AUA new technology assessment committee[9].

The Kolmogorov-Smirnov goodness-of-fit test was used to examine whether a variable was distributed normally All parameters are reported as mean with standard deviation (SD). Further statistical analyses were done with Chi-square test, one-way ANOVA, the Kruskal-Wallis test, Student's t-test, Mann-Whitney *U* test and Wilcoxon signed ranks test. Significance was set at 5 percent. Statistical analyses of long-term data were only performed with earlier data from the same patients or between different treatment modalities.

Results

Initially, 50 men were randomized for TURP, 45 for laser and 46 for electrovaporization. For various reasons patients were not suited for further evaluation directly postoperatively or during the course of their first year postoperatively[4,5] (see table 1).

After 1 year, there were still 41 TURP patients, 37 laser patients and 34 electrovaporization patients available for further follow-up, making a total of 112 patients.
In fall 2002, ninety-eight patients or relatives responded finally (response rate 88%). Fourteen (12%) patients did not respond at all (table 1). Seventeen percent of the responders had been reoperated, was not willing to cooperate, died or could not be evaluated due to morbidity (table 1). Eighty-one responding patients (83% of the responders) returned all questionnaires and these could be used for long-term analysis (83% of the responders). Fifty-nine responding patients performed free uroflowmetry (60% of the responders).
The follow-up time varied individually, because all patients were analyzed in about two months. Depending on individual follow-up time, patients were divided into two groups: follow-up time between 1-4 years and follow-up time between 4-7 years. In the TURP group 15 patients were analyzed after 1-4 years and another 15 patients after 4-7 years with a mean follow-up of 2.7 ± 0.8 and 5.7 ± 0.8 years respectively and age 66.8 ± 8.2 and 70.5 ± 7.9 years respectively. In the laser group 10 and 17 patients were analyzed after 1-4 years and 4-7 years respectively with a mean follow-up of 2.6 ± 0.9 and 5.5 ± 0.7 years respectively and age 65.3 ± 11.0 and 72.3 ± 8.3 years respectively. In the electrovaporization group 12 patients were analyzed after 1-4 years and another 12 patients after 4-7 years with a mean follow-up of 2.8 ± 1.0 and 5.4 ± 1.0 years respectively and age 64.4 ± 8.2 and 71.3 ± 11.6 years respectively. Preoperative baseline values of the patients analyzed after 1-4 years did not show any significant differences with those of the patients analyzed after 4-7 years. There were no significant differences in age and follow-up time between the different treatments.
Schäfer obstruction grades during inclusion were for TURP, laser and Vaportrode 3.5 ± 1.1, 3.4 ± 1.2 and 3.6 ± 1.1 respectively. Prostate volumes at that time were 37 ± 11, 38 ± 9 and 35 ± 12 ml respectively. There were no significant differences between the different treatment groups.
In table 2 the results of frequencies, maximum flow and AUA questionnaires are represented. Graphic representations of these results are shown in figures 1-3.
Only preoperative and six and twelve months data of those patients are listed who were also seen at long-term follow-up. There were no significant differences between the different treatment groups at baseline, except for maximum flow.
There were no significant differences for the number of voidings during daytime between the treatments at any time point. Nocturia also never showed significant differences between the treatments. However, in the laser group there was a significant higher nocturia (mean 1.9) in the 4-7 years group ($p=0.05$).
Forty-six out of 59 patients (78%) who performed uroflowmetry were able to void more than 150 ml. Maximum free uroflow showed lower values in both long-term follow-up groups compared to earlier values. In the TURP and electrovaporization

Table 1 Reasons why patients dropped out from further follow-up during the course of the investigations.

	TURP	Contact Laser	Vapor trode
Included patients at baseline	50	45	46
Procedure during surgery changed for medical reasons	0	3	2
Surgery canceled due to other medical problems	1	0	1
Equipment failure resulting in standard therapy (TURP)	-	2	1
Procedure during surgery not correctly performed	0	0	4
Mortality within first postoperative year	2	0	0
Morbidity making follow-up impossible within first postoperative year	2	0	1
Patient emigrated within first postoperative year	1	0	0
Reoperation (TURP) within first postoperative year	2	1	2
Reoperation because of urethral stricture within first postoperative year	1	2	1
Suitable for further evaluation after one postoperative year	41	37	34
No response in fall 2002	4	5	5
Number of responders in fall 2002	37	32	29
Reoperated (TURP)	1	2	2
Reoperated because of urethral stricture	1	0	0
Morbidity making further follow-up impossible	2	0	0
Not willing to cooperate	1	0	1
Number of men died	2	3	2
Suitable for further evaluation	30	27	24

Table 2 Subjective scores from AUA questionnaires, maximum uroflowmetric results and frequency during daytime and nighttime, of patients analyzed during follow-up. Data presented as mean with SD.

	Baseline	6 months	1 year	1-4 years	4-7 years
Frequency during daytime					
TURP	9.1 ± 4.2	7.1 ± 1.7	6.3 ± 1.9	6.7 ± 2.8	5.8 ± 3.5
Laser	9.2 ± 4.0	6.9 ± 2.3	5.1 ± 1.5	7.6 ± 2.5	6.2 ± 2.0
Vaportrode	8.9 ± 2.6	6.5 ± 2.1	6.7 ± 3.2	5.8 ± 2.1	5.7 ± 1.7
Frequency during nighttime					
TURP	2.4 ± 1.5	1.1 ± 0.8	1.1 ± 0.6	0.9 ± 0.9	1.1 ± 0.6
Laser	2.8 ± 1.4	1.6 ± 0.9	1.6 ± 0.8	1.4 ± 1.1	1.9 ± 1.1
Vaportrode	2.1 ± 1.5	0.9 ± 0.8	0.9 ± 0.6	1.1 ± 1.2	1.0 ± 0.9
Maximum flow (ml/s)					
TURP	13 ± 4	26 ± 6	23 ± 10	20 ± 5	17 ± 8
Laser	9 ± 3	25 ± 9	27 ± 12	19 ± 6	19 ± 9
Vaportrode	9 ± 3	24 ± 11	28 ± 6	23 ± 6	16 ± 11
Symptom Score Index					
TURP	16.6 ± 5.6	3.2 ± 2.7	4.1 ± 4.8	5.8 ± 7.5	7.3 ± 7.1
Laser	18.3 ± 8.2	5.9 ± 5.5	3.6 ± 3.4	9.3 ± 5.2	8.3 ± 6.4
Vaportrode	20.3 ± 6.8	3.8 ± 2.7	4.8 ± 4.9	8.4 ± 8.7	7.0 ± 5.6
Symptom Problem Index					
TURP	12.5 ± 6.2	1.0 ± 1.8	1.4 ± 2.8	4.2 ± 6.9	4.5 ± 7.6
Laser	11.9 ± 7.7	2.4 ± 4.0	1.1 ± 1.6	3.0 ± 3.5	4.6 ± 5.3
Vaportrode	14.6 ± 7.3	1.8 ± 2.2	3.0 ± 4.7	2.5 ± 5.2	3.6 ± 3.9
Quality of Life Score					
TURP	3.9 ± 1.6	0.5 ± 0.5	0.6 ± 0.8	1.1 ± 1.2	1.3 ± 1.3
Laser	3.6 ± 1.6	0.8 ± 1.0	0.6 ± 0.9	2.0 ± 1.0	1.4 ± 1.2
Vaportrode	4.3 ± 1.3	1.0 ± 0.8	1.0 ± 0.9	1.0 ± 1.2	1.4 ± 0.8
BPH Impact Index					
TURP	9.1 ± 4.7	0.8 ± 1.2	1.4 ± 2.1	2.3 ± 3.4	2.9 ± 3.8
Laser	8.8 ± 3.8	2.8 ± 3.2	1.5 ± 2.0	4.1 ± 3.1	3.3 ± 3.1
Vaportrode	11.1 ± 4.0	2.5 ± 2.3	2.7 ± 3.0	2.1 ± 3.3	2.9 ± 2.3

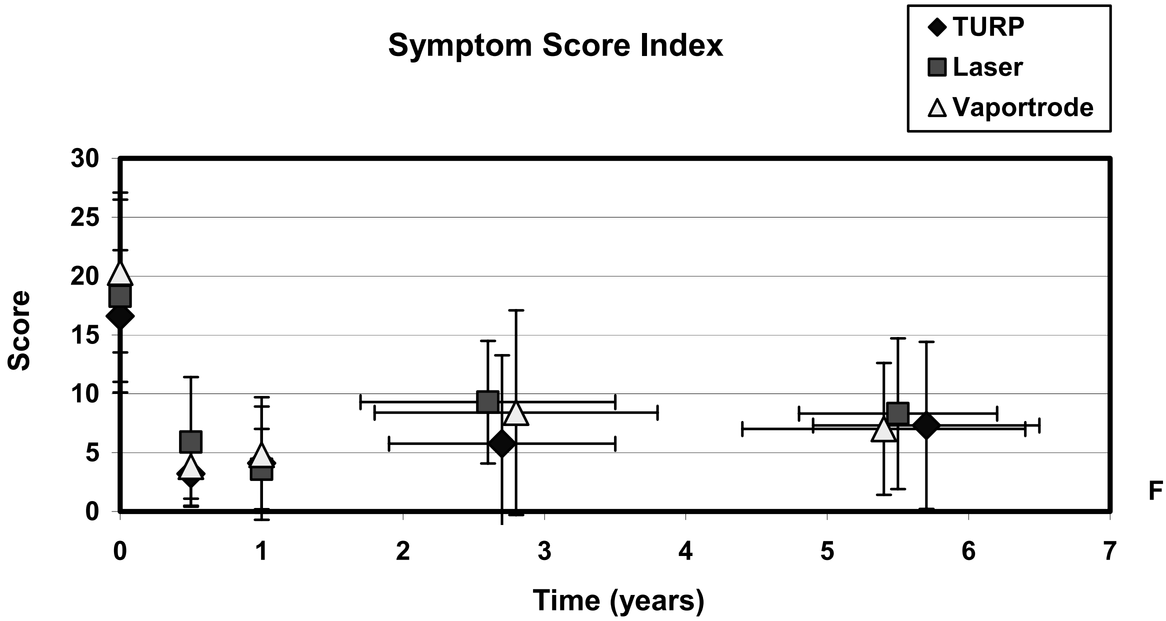

Figure 1a Symptom score index at baseline and during follow-up. Data are presented as mean with standard deviation.

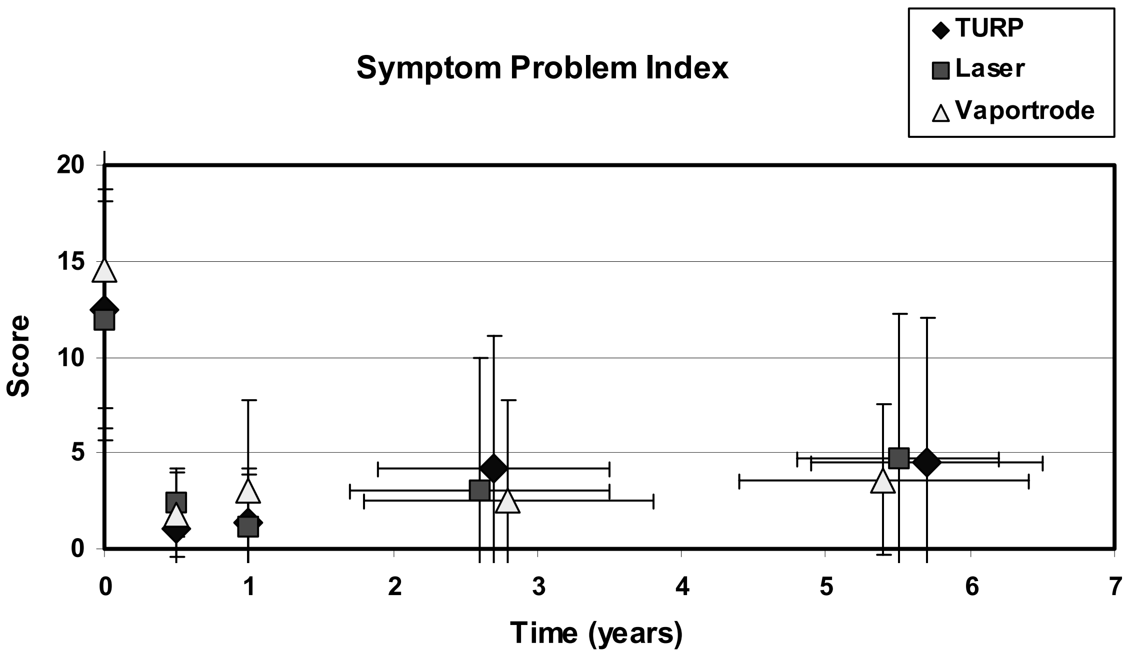

Figure 1b Symptom problem index at baseline and during follow-up. Data are presented as mean with standard deviation.

Figure 1c Quality of life score at baseline and during follow-up. Data are presented as mean with standard deviation.

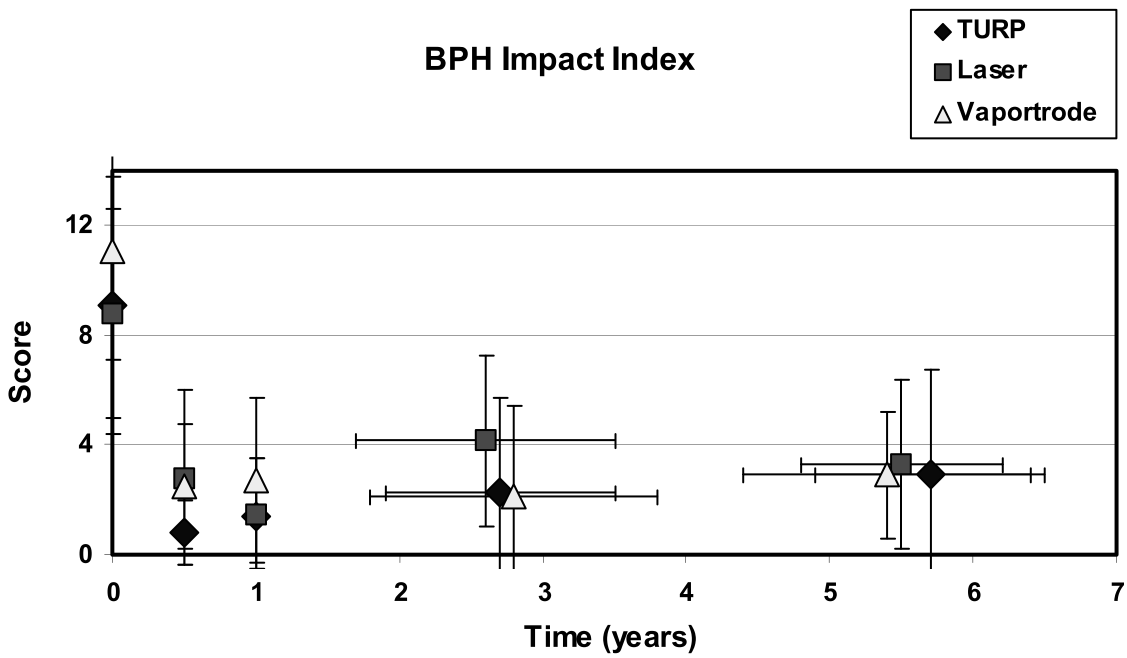

Figure 1d BPH impact index at baseline and during follow-up. Data are presented as mean with standard deviation.

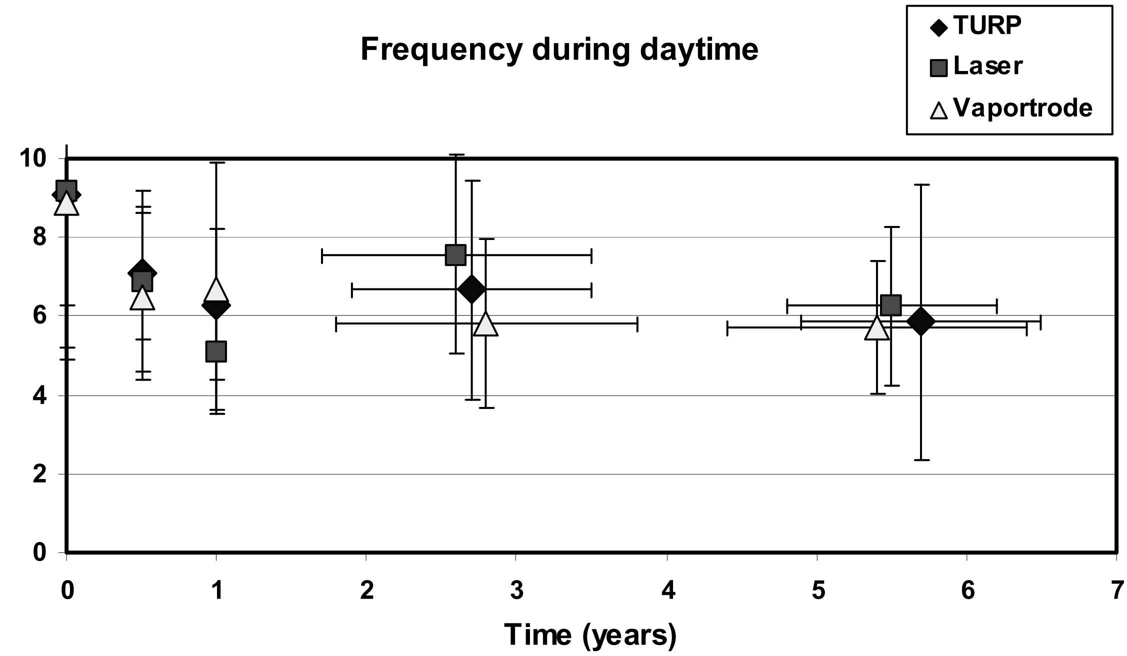

Figure 2a Frequency during daytime at baseline and after follow-up. Data are presented as mean with standard deviation.

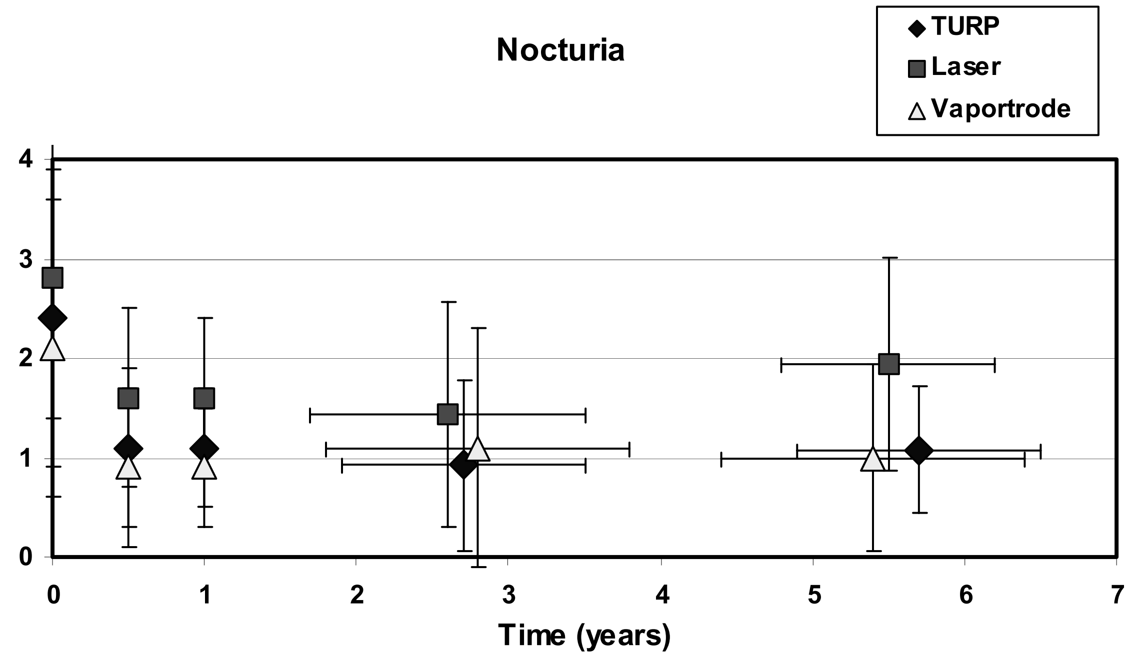

Figure 2b Frequency during nighttime at baseline and after follow-up. Data are presented as mean with standard deviation.

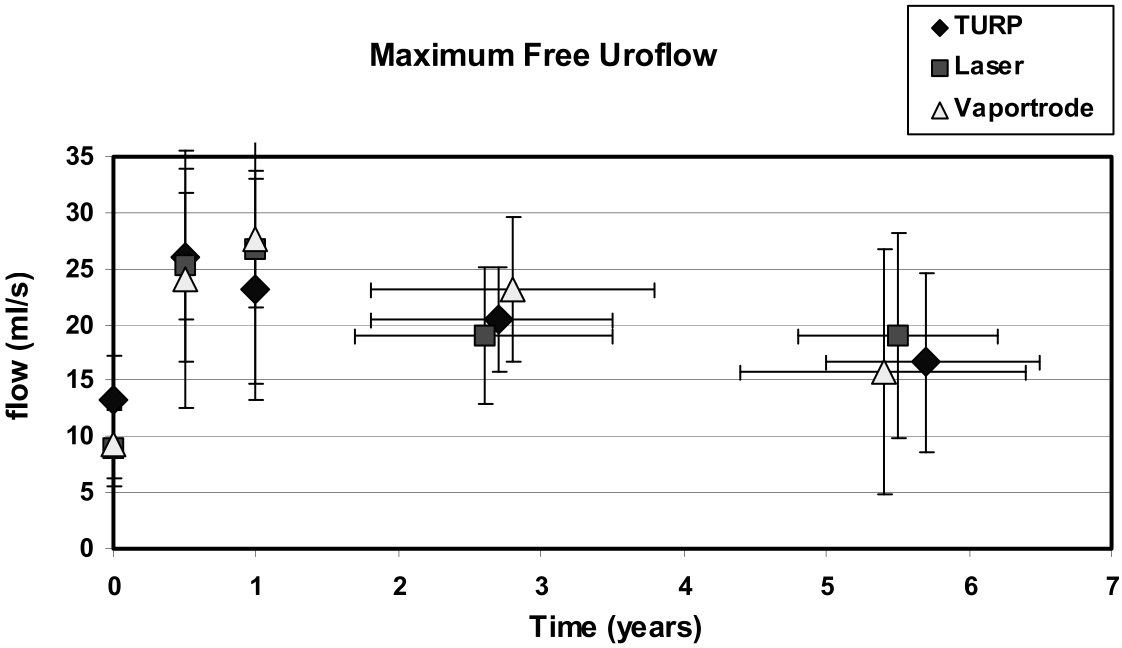

Figure 3 Maximum free uroflow rate at baseline and after follow-up. Data are presented as mean with standard deviation.

group, results after 1-4 years follow-up were significantly higher compared to their preoperative values. In the laser group, results after 4-7 years were significantly higher than preoperatively. However, there are no significant differences between the different methods for prostatectomies at any time interval.

International Prostate Symptom Score index (IPSS), Symptom Problem index (SPI), the Quality of Life score (QoL) and BPH Impact Index (BII) show slight, but not significant, increases during long-term follow-up

There are no significant differences between the treatment groups. All values, at both follow-up times, are significantly lower than pre-operative values, except for laser patients after 1-4 year follow-up (p between 0.07 and 0.10).

The incidences of pain during voiding, lower abdomino-genital pain, hesitation or haematuria were in all groups during long-term follow-up between 0-5%. There was a small increase in urgency, with an incidence of 15 to 22%, although the ‘severity x duration’ product was low, about 2.3 in all treatment modalities. The incidences of incontinence were 8%, 39% and 15% in the TURP, laser and electrovaporization group respectively. The high incidence in the laser group was accompanied by a ‘severity x duration’ product of 3.7 (maximum 35), indicating only incidental small urine loss. This number is comparable with those in the TURP and electrovaporization groups: 2.5 and 3.3 respectively.

In the period after the first postoperative year, 1 TURP patient underwent a second TURP, and 2 patients each underwent TURP in the laser and electrovaporization groups. Including the reoperations in the first postoperative year (table 1), reoperation rates after a mean follow-up of 4.3 years for TURP, laser and electrovaporization were 6%, 7% and 9% respectively. There was one urethral stricture in the TURP group after one year and this was not seen in the other groups. Seven patients (7%) died more than 1 year postoperatively according to relatives who responded (table 1). Including mortality in the first postoperative year, mortality rates after a mean follow-up of 4.3 years were for TURP, laser and electrovaporization 8%, 7% and 4% respectively. These deaths were not related to their prostatic surgery or related to BPH complications.
Two patients were excluded because of morbidity (2%): both for prostatic carcinoma. Two were not willing to cooperate (2%): both patients were not satisfied with the results.

Comment

At 1 year postoperatively we were able to further evaluate 112 of the initially 141 included patients. Table 1 lists the reasons why the remaining 29 patients could not be evaluated. Of these 112 patients finally 14 did not respond. This means that 14 patients were lost–to-follow-up of the initially 141 included patients. The response rate of 88% enabled an adequate follow-up. However, patients were only analyzed once after their one year follow-up. This results in a large variation in individual follow-up time varying from 1.5 to 7.0 years. Secondly, the low number of patients creates a low power, so that significant differences might not always be detected. In each treatment group there were 24-30 patients scattered over the long time interval, with 2-6 patients per follow-up year. Therefore, patients were divided over two follow-up time intervals of 3 years each: a follow-up time of 1-4 years and a follow-up time of 4-7 years. In this way, data can be presented and interpreted more comprehensibly. Statistical analyses were only performed on data from patients who were seen at baseline and at long-term follow-up. Although the two groups consist of different patients (with similar baseline values), we still think this division is meaningful, because there is a large time difference between the two groups.
The results of this follow-up demonstrate a high durability for symptomatic and subjective relief. The various AUA validated questionnaires show only a small rise with no statistical significant differences between the treatment modalities. This rise might partially be explained by normal aging during which symptoms and bothering increase. IPSS index in the Olmsted County study increased with 0.44 units per year for men in the sixties[10]. An equivalent study in the Netherlands also showed a significant increase in IPSS with age[11].

Frequencies during daytime and nighttime were for all groups during long-term follow-up very similar compared to the values 1 year Postoperatively. We have no good explanation for the significant higher mean nocturia (1.9) in laser patients after 4-7 years.

The number of patients evaluated by uroflowmetry is limited, because not all patients were able to visit the outpatient department due to the high age of a number of patients. Maximum uroflow showed lower values after long-term follow-up: about 20 ml/sec. after 1-4 years and between 16 and 19 ml/sec. after 4-7 years follow-up. These decreases can not be fully explained by normal aging as was observed in the Olmsted County Study[12,13]. Cross sectional data from this study showed mean maximum flows of about 15.5 ml/sec. and about 14 ml/sec. for age groups of 65-69 years and 70-74 years respectively. Annualized percent decrease in the 60-69 years and 70-79 years age groups were 2.3% and 6.5% respectively.

Follow-up results from AUA questionnaires and maximum uroflow are compared to data from men without a history of prostatic disease. Comparison to these data is difficult, because a surgical intervention might interfere with normal aging processes of bladder and prostate.

The specific morbidity and symptom questionnaires demonstrated few differences between the treatment groups and most parameters were scored only incidentally. Urgency and incontinence showed higher values. The 39% incidence of incontinence in the laser group is much higher than in the other groups, although the ‘severity x duration’ products are low and very similar in all groups.

Several other studies have analyzed long-term results of laser and electrovaporization. Keoghane et al published 3 and 5-year data from the Oxford laser prostatectomy trial[14,15], comparing laser with TURP. Initially 152 patients were randomized. After follow-up times of 3 and 5 years, eighty-seven (57%) and fifty-seven (38%) patients were available for further analysis. IPSS after 3 and 5 years are comparable to results of the present study. Maximum uroflow was slightly lower with 14.0 ml/sec. after 5 years for both TURP and laser. Reoperation rates were higher: 18% for laser and 14.5% for TURP. In a non-randomized study, Floratos[16] analyzed results of laser after a median follow-up time of 3.9 years. IPSS and Quality of life showed stable results, similar to the present study, but maximum uroflow progressively worsened to a median of 11.1 ml/sec after about 4 years. Retreatment rate was 14%.

Long-term electrovaporization results were published by Hammadeh et al[17]. They demonstrated durable results comparing TURP with Vaportrode after 3 years follow-up. IPSS and Quality of Life results after 3 years were very similar to results after one year. The same was demonstrated for maximum flows, which were 18.0 ml/sec. and 22.2 ml/sec. for TURP and electrovaporization respectively after 3 years. Reoperation rate after 3 years was 13% for electrovaporization. There were no significant differences between the treatments.

We found no clinically relevant differences between the treatment groups during long-term follow-up. Today in our clinic, TURP is still often used as a treatment modality. However, contact laser prostatectomy is used on a regular basis for high risk patients, because of the low blood loss during surgery. A selected group of men is more and more treated with laser prostatectomy in a day care setting.

Conclusions

This up to seven years follow-up, demonstrates in general durable subjective and objective results for patients with LUTS associated with BPH after TURP, contact laser or electrovaporization. IPSS, SPI, QoL and BII increase slightly and maximum uroflow decreases to about 150% of the preoperative values. There are no clinically relevant differences between the different treatment groups during long-term follow-up.

References

1. Holtgrewe, H.L.: Current trends in management of men with lower urinary tract symptoms and benign prostatic hyperplasia. Urol. suppl 4A, 51: 1-7, 1998.

2. Mebust, W.K., Holtgrewe, H.L., Cockett, A.T., et al: Transurethral prostatectomy: immediate and post-operative complications. A cooperative study of 13 participating institutions evaluating 3885 patients. J. Urol. 141: 243-247, 1989.

3. Doll, H.A., Black, N.A., McPherson, K., et al: Mortality, morbidity and complications following transurethral resection of the prostate for benign prostatic hypertrophy. J. Urol. 147: 1566-1573, 1992.

4. Van Melick, H.H., van Venrooij, G.E., Eckhardt, M.D., et al: A randomized controlled trial comparing transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia: urodynamic effects. J. Urol. 168: 1058-1062, 2002.

5. Van Melick, H.H., van Venrooij, G.E., Eckhardt, M.D., et al: A randomized controlled trial comparing transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia: analysis of subjective changes, morbidity and mortality. J. Urol. 169: 1411-1416, 2003.

6. Chatelain, C., Denis, L., Foo, K.T., et al: Recommendations of the international scientific committee: Evaluation and treatment of lower urinary tract symptoms (LUTS) in older men. In: Benign Prostatic Hyperplasia, Proceedings of the 5th International Consultation on BPH. edition 2001, Plymouth, UK, Plymbridge Distributors, 2001, pp 519-534.

7. Barry, M.J., Fowler jr., F.J., O'Leary, M.P., et al: The American Urological Association symptom index for benign prostatic hyperplasia. J. Urol. 148: 1549-1557, 1992.

8. Barry, M.J., Fowler jr., F.J., O'Leary, M.P., et al: Measuring disease-specific health status in men with benign prostatic hyperplasia. Med. Care suppl 4, 33: AS145-155, 1995.

9. Holtgrewe, H.L.: Guidance for clinical investigation of devices used for the treatment of benign prostatic hyperplasia. J. Urol. 150: 1588-1590, 1993.

10. Guess, H.A., Chute, C.G., Garraway, W.M., et al: Similar levels of urological symptoms have similar impact on Scottish and American men-although Scots report less symptoms. J. Urol. 150: 1701-1705, 1993.

11. Bosch, J.L., Hop, W.C., Kirkels, W.J., et al: The international prostate symptom score in a community-based sample of men between 55 and 74 years of age: prevalence and correlation of symptoms with age, prostate volume and residual urine volume. Brit. J. Urol. 75: 622-630, 1994.

12. Girman, C.J., Panser, L.A., Chute, C.G., et al: Natural history of prostatism: urinary flow rates in a community-based study. J. Urol. 150: 887-892, 1993.

13. Roberts, R.O., Jacobsen, S.J., Jacobson, D.J., et al: Longitudinal changes in peak urinary flow rates in a community based cohort. J. Urol. 163: 107-113, 2000.

14. Keoghane, S.R., Lawrence, K.C., Gray, A.M., et al: A double-blind randomized controlled trial and economic evaluation of transurethral resection vs contact laser vaporization for benign prostatic enlargement: a 3-year follow-up. Br. J. Urol. 85: 74-78, 2000.

15. Keoghane, S.R., Sullivan, M.E., Doll, H.A., et al: Five-year data from the Oxford Laser Prostatectomy Trial. Br. J. Urol. 86: 227-228, 2000.

16. Floratos, D.L., Sonke, E.E., Franciska, E.A., et al: Long-term follow-up of laser treatment for lower urinary tract symptoms suggestive of bladder outlet obstruction. Urol. 56: 604-609, 2000.

17. Hammadeh, M.Y., Madaan, S., Singh, M., et al: A 3-year follow-up of a prospective randomized trial comparing transurethral electrovaporization of the prostate with standard transurethral prostatectomy. Br. J. Urol. 86: 648-651, 2000.

Cost aspects of transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia

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Urology, accepted

Abstract

Purpose: To compare costs of transurethral resection of the prostate (TURP), contact laser prostatectomy (CLP) and electrovaporization in men with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

Materials and Methods: A randomized controlled trial was conducted. Included were men with LUTS, who met the criteria of the International Scientific Committee on BPH. Subjective changes were quantified using questionnaires validated by the American Urologic Association (AUA). Maximum free urinary flow rate was estimated. Morbidity and mortality were registered. These parameters were measured at regular intervals up to one year and once during long-term follow-up. A cost analysis together with a sensitivity analysis was performed based on a follow-up of 12 months.

Results: Fifty men were randomized for TURP, 45 for laser treatment and 46 for electrovaporization. Subjective and objective changes were very similar during the 12 months follow-up. Costs were highest for CLP and lowest for electrovaporization. However, hospital stay decreased during trial more for CLP and electrovaporization than for TURP. Recalculations demonstrated almost equal costs for CLP and TURP and lowest costs for electrovaporization.

Conclusions: Electrovaporization has lower costs than CLP and TURP in patients with LUTS associated with BPH. CLP and TURP show very similar costs.

Introduction

From a physician's point of view one would like to offer a patient an optimal treatment; that is the combination of a maximum relief of symptoms and bothering with a minimum of morbidity. However, to suggest that medical decision making can be divorced from consideration of costs, denigrates the complexity of patient care. Choices must be made between alternative treatments and these decisions must be based on both costs and outcomes[1].

These choices are becoming more and more important in treatment of men with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Resources are limited and there is an increase in patients presenting with LUTS together with an increase in treatment modalities.

Since the early 1990[s], a plethora of new minimally invasive therapies has been introduced to treat men with LUTS associated with BPH. Most studies have been conducted to analyze the clinical outcome results of these surgical therapies. Only a few performed a cost-effectiveness analysis or other types of economic analyses. Until 1996, there were only fourteen papers identified that performed some type of economic analysis[2]. Only eight of these satisfied more than half of the criteria given by Drummond et al regarding the assessment of economic evaluations[3]. Today, economic analysis is recommended by the committee on the economics of BPH of the international consultation on BPH[4]. Several data are available about medical therapy, TURP, contact and non-contact laser therapy and some other minimally invasive therapies[5-12].

At our clinic, a randomized controlled study comparing transurethral resection of the prostate (TURP), contact laser prostatectomy (CLP) and electrovaporization (Vaportrode) has been done in men with LUTS associated with BPH. Previously, we published the urodynamic changes six months postoperatively[13] and subjective and symptomatic changes at various time intervals up to a maximum of seven years postoperatively, together with morbidity and mortality[14,15]. Improvements, morbidity and mortality of the three treatment modalities were very similar. In order to compare these treatments economically, a cost analysis has been performed, including a sensitivity analysis.

Material and methods

A prospective randomized controlled study was carried out between 1996 and 2001 at our clinic. Detailed descriptions of inclusion and exclusion criteria, together with details about used materials, operation techniques and measurement techniques are published previously[13-15]. Included were men over 45 years of age with LUTS associated with BPH. Patients were randomized between TURP, contact laser prostatectomy and electrovaporization (Vaportrode). Symptomatic and subjective results were analyzed using questionnaires[16,17] validated by the American Urological Association (AUA). Patients completed the International Prostate Symptom Score Index (IPSS), the Symptom Problem Index (SPI), the BPH Impact Index (BII) and the Quality of Life (QoL) question. Uroflowmetry was performed to estimate maximum flow. Morbidity and mortality were registered. These questionnaires and tests were used preoperatively and postoperatively at regular intervals including 6 months and 1 year. In a long-term follow-up, the same parameters were studied once in each patient at an individually varying time interval with a mean of 4.3 years[15].

Primary outcomes were IPSS, SPI, BII, QoL score and maximum flow. There were no clinical relevant differences for these outcomes between the three treatment modalities up to one year[13] and during long-term follow-up[15]. Morbidity and mortality were also very similar[14]. Significant changes were seen in operative parameters, like a shorter duration in hospital stay for electrovaporization and less blood loss in laser treatment[14].

An analysis is made of costs included in the different treatment modalities. Statistical evaluation of these costs is not performed, because several assumptions are made to calculate these costs. The margins of these assumptions are sometimes unclear, which makes statistical evaluation complicated, unreliable and therefore does not provide useful information. The cost analysis is from a health care perspective.

Collection and valuation of resource use data

a) Personal time in operating theater: costs per treatment were calculated using annual salaries adjusted for real time spent on direct patient care. One urologist and one urology trainee were counted for the full operating time, one anesthesist was counted for his time with the patient, two surgeon assistants and one anesthesist assistant were counted for the full time a patient was in the operating theater. Overhead costs for the operating theater are 41% and are presented separately.

b) Use of surgical equipment for TURP, laser and electrovaporization: capital equipment is valued using 2003 market prices. Life-spans for electro-generators and laser-generator were assumed to be 7 years. Opportunity costs of 5% per annum were assumed. Costs for service and maintenance are added. Electro-generators and laser-generators are also used for several other types of urological surgery, e.g. transurethral electroresection or laser coagulation of bladder carcinoma, laser coagulation of condylomata acuminata or incisions of the bladder neck. In this way, a percentage of the specific use for prostate surgery (allocation rate) was calculated for both generator types. Initial calculations were based on allocation rates of 51%, 29% and 60% for TURP, laser and electrovaporization respectively. Consumables for TURP (resection loops), laser (fibers and tips) and electrovaporization (vaporization wheels) are valued at 2003 market prices. Laser fibers were used on average 2.5

times, resection loops 25 times and vaporization wheels 5 times each. Costs for sterilization and maintenance were added.

c) Perioperative hospital stay and use of resources: all patients received intraoperatively antibiotics intravenously and postoperatively analgesics. Blood analysis regarding haemoglobin and electrolytes was performed several times during hospital stay. Costs for hospital stay including overhead costs were calculated per day using data from the finance department.

e) Inpatient rehospitalization: all surgery related complications were registered. Costs were calculated in the same way as mentioned before.

Sensitivity analysis

Valuation of resource use data is partially based on assumptions. Small changes in these assumptions can sometimes cause large differences in costs. Accuracy for several assumptions is hard to make and calculations incorporate often indirect estimations of costs. Dayprices for hospital stay vary over short time and overhead costs can only be estimated by subtraction of total costs by certain specified costs. An important factor in total costs per treatment is hospital stay. This changed during the years the trial was one. Therefore, a recalculation with different values is performed. A mean long-term follow-up of 4.3 years demonstrated a change in reoperation rates (re-TURP) compared to those after 12 months[15]. Recalculations have been made with these long-term rates. Life span of equipment might change, because technological advances are made rapidly. Recalculations have been made with a 4 year life spans for all equipment. Another complicating factor is the percentual allocation of machinery to prostatectomies. These rates are mentioned before and represent the time that the electro-generator or laser-generator was used for prostatectomies during the course of the study in our center. Especially the laser rate might change because new developments might change allocation. Recalculations have been made with 40% and 80% rates for laser.

Costs are presented in Euros (€). Statistical analyses were performed with ANOVA and Student's t-test. Data are presented as means with standard deviation (SD).

Results

Table 1 shows the preoperative major outcome results and those after 12 months, together with the absolute and percentual change in these results. Statistical analysis did not show any significant differences at baseline or after 12 months between the treatment groups for these parameters, nor were there significant differences in the changes of these parameters in 12 months between the different treatment groups[14].

Resource use data for staff operation time was 58±26 min, 58±11 min and 50±16 min for TURP, laser and electrovaporization respectively. Nurse operation time was

Table 1 Results at baseline and after 12 months follow-up including change for the different treatment groups. Data presented as mean ± SD.

	Baseline	12 months Posttreatment	Absolute change (percent change)
Symptom Score Index			
TURP	16.8 ± 6.0	4.6 ± 4.8	-12.2 (-73%)
Laser	18.9 ± 6.8	5.8 ± 5.7	-13.1 (-69%)
Electrovaporization	20.2 ± 6.6	6.7 ± 6.4	-13.5 (-67%)
Symptom Problem Index			
TURP	11.9 ± 6.7	2.4 ± 4.7	-9.5 (-80%)
Laser	12.5 ± 7.8	2.4 ± 3.3	-10.1 (-81%)
Electrovaporization	14.1 ± 6.7	4.2 ± 5.2	-9.9 (-71%)
Quality of Life score			
TURP	3.8 ± 1.5	0.9 ± 1.2	-2.9 (-76%)
Laser	3.7 ± 1.6	1.0 ± 0.9	-2.7 (-74%)
Electrovaporization	4.1 ± 1.4	1.4 ± 1.4	-2.7 (-65%)
BPH Impact Index			
TURP	9.6 ± 4.7	2.4 ± 3.8	-7.2 (-75%)
Laser	9.3 ± 4.2	2.0 ± 2.2	-7.3 (-78%)
Electrovaporization	10.8 ± 4.1	3.8 ± 4.1	-7.0 (-65%)
Maximum flow (ml/sec.)			
TURP	11.4 ± 3.7	21.4 ± 8.4	+10.0 (+88%)
Laser	11.5 ± 4.1	22.0 ± 11.2	+10.5 (+91%)
Electrovaporization	10.8 ± 4.2	22.7 ± 8.3	+11.9 (+110%)

93±38 min, 86±26 min and 85±32 min for TURP, laser and electrovaporization respectively. Hospital stay was 3.9±0.9 days, 3.8±1.3 days and 3.4±0.9 days for TURP, laser and electrovaporization respectively. The reoperation rate (re-TURP) was 4.0%, 2.2% and 4.3% within 12 months for TURP, laser and electrovaporization respectively.

Calculated costs per patient are listed in the upper part of table 2. Costs of operating room equipment were almost similar between TURP and electrovaporization, but more expensive for laser equipment. This resulted in laser being the most expensive treatment (€ 1714), followed by TURP (€ 1552) and electrovaporization (€ 1354) being the cheapest.

The results of a sensitivity analysis are represented in the lower part of table 1. Significant decreases in hospital stay were observed more in laser and electrovaporization patients than in TURP patients during the trial. Hospital stay for laser and electrovaporization patients were 3.8 and 3.4 days respectively, and 3.9 days for TURP patients. For all treatment modalities there was a reduction in this

Table 2 Costs in Euros (€) per patient after 12 months follow-up for the three different treatments. A sensitivity analysis is included showing the costs after recalculations with different assumptions.

	TURP	Contact Laser	Electro-vaporization
Operation time: staff	€ 232	€ 232	€ 206
Operation time: nurses	€ 171	€ 158	€ 156
Consumables	€ 19	€ 194	€ 30
Overhead operating theater	€ 173	€ 235	€ 160
Theater costs	€ 595	€ 809	€ 550
Post-operative hospital stay	€ 695	€ 679	€ 615
Consumables	€ 129	€ 130	€ 118
Re-operations including re-hospitalization	€ 133	€ 95	€ 71
Post-operative costs	€ 957	€ 904	€ 804
Total costs	**€ 1552**	**€ 1714**	**€ 1354**
Total costs with different assumptions			
Hospital stay last 2 years	€ 1494	€ 1526	€ 1260
Re-TURP rates 6.0%, 6.7% and 8.7%[1]	€ 1519	€ 1589	€ 1311
Life span equipment 4 years[1]	€ 1502	€ 1550	€ 1270
Allocation laser 40%[1]	€ 1494	€ 1545	€ 1260
Allocation laser 80%[1]	€ 1494	€ 1611	€ 1260

Recalculations based on hospital stay of the last two years of the trial.

number of hospital days when comparing with the last two trial years. Values of hospital stay during the last 2 years of the trial were 3.6 days, 2.9 days and 2.8 days for TURP, laser and electrovaporization patients respectively. Costs for laser become more equal to costs for TURP, while electrovaporization is still the cheapest. All other recalculations are made with values for hospital stay during the last 2 years. Rates for re-TURP were previously demonstrated during long-term follow-up[15]. All extra recalculations have only small effects on total costs: electrovaporization is always cheapest and laser costs are almost similar to TURP costs.

Discussion

Previous publications about this trial showed that the three treatment modalities showed similar symptomatic, subjective and objective results after 12 months. Even after a mean follow-up of 4.3 years subjective and objective results were very similar. Analysis of morbidity also demonstrated only small differences between the three treatment modalities[13-15]. As mentioned in the introduction, resources are scarce in today's world and outcome results should be compared to their costs, before making treatment decisions. The economic analysis of our trial demonstrates relevant differences between the costs of TURP, contact laser and electrovaporization. The initially calculated costs are best for electrovaporization and better for TURP compared to contact laser. An important observation was made regarding hospital stay: there were significant decreases for all treatment modalities during the time the trial was on, but these were larger for laser and electrovaporization patients. A too careful regimen regarding hospital stay might have been used in the first years, because one had to become confident with the postoperative results of these new techniques. Hospital stay data of the last two years together with reoperation rates observed during long-term follow-up demonstrate that electrovaporization has still the lowest costs, and laser and TURP results are very similar. Other recalculations are all based on these hospital stay values, because these are assumed to be most realistic for the future. Maybe hospital stay can even be reduced more in a selected group of patients. Several patients have been operated with good results using contact laser in daycares setting or they were discharged within 24 h. Mueller[9] presented a study of 50 consecutively operated patients with contact laser. Ninety-six percent was discharged within 24 h without catheter. Other recalculations with a shorter life time for (laser) equipment, re-TURP rates based on long-term results or different allocation rates hardly changed the total costs.

Postoperative follow-up includes reoperations and rehospitalizations, but not outpatient follow-up. The latter might be an important factor, but this can hardly be demonstrated in this trial. Patients were seen according to the trial protocol on a regular base. In this way it is difficult to differentiate between visits that were made because of our protocol or because there was a medical need for an extra visit. However, large differences are not expected, because of two reasons. Analysis of the total number of outpatient visits postoperatively did not show significant differences between the treatment groups. Secondly, analysis of morbidity with weekly patient questionnaires during six weeks postoperatively and after 3, 6 and 12 months did not demonstrate clinically relevant differences among the three treatment modalities.

This evaluation does not report all data involved in an economic analysis as recommended by the committee on the economics of BPH from the international

consultation on BPH[4]. These cost data should also include patient costs and costs of lost productivity from the workplace. In a study regarding non-contact laser treatment, patient costs were only of minor importance to the total costs[5]. Costs of lost productivity might have a relevant influence, but is more difficult to quantify. In the present study, about 70% was 60 years of age or more. A substantial number of patients contributed to lost productivity, though we did not quantify these costs.
There are no other publications about economic analyses regarding electrovaporization. Keoghane et al have published an economic analysis about the use of contact laser prostatectomy in the Oxford laser trial, which compares contact laser with TURP[7,8]. Comparisons with other analyses are difficult, because assumptions are different and not always known, prices are valued to other years and there are differences in currency. Theater consumables in the Oxford laser trial (1997 prices) were £67 for TURP and £311 for contact laser. The percentual difference is much larger than in the present study, which might reflect diminishing costs for laser consumables. Total costs (including costs for the operating theater, hospital stay, community, capital services and re-operations) were £971.4 for TURP and £1252.2 for contact laser treatment. These are 29% higher costs for laser, which is a much larger difference than the 10% higher costs for laser (table 1) in the present study. Mueller[9] published average costs of contact laser that were very similar to costs for TURP. Equipment costs were highest for laser, but 96% was discharged within 24 h. There are however, no detailed calculations of these costs.
Recently, Noble et al[5] published a similar economic evaluation comparing TURP, side fire (non-contact) laser ablation and conservative management. They concluded that for symptomatic improvement non-contact laser treatment was the most costly modality with lower cost-effectiveness ratios than TURP.

Conclusions

Evaluation after 12 months and even after long-term follow-up demonstrates very similar subjective and objective results between men with LUTS associated with BPH after TURP, contact laser prostatectomy or electrovaporization. Costs for laser equipment are higher than for TURP and electrovaporization. Shorter hospital stay for laser and electrovaporization make total costs for laser similar to costs for TURP and make total costs for electrovaporization lowest.

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References

1. Eisenberg, J.M.: Clinical economics. A guide to the economic analysis of clinical practices. JAMA, 262: 2879-2886, 1989.

2. Kortt, M.A. and Bootman, J.L.: The economics of benign prostatic hyperplasia treatment: a literature review. Clin. Ther., 18: 1227-1241, 1996.

3. Drummond, M.F., Stoddart, G.L. and Torrance, G.W.: Methods for the economic evaluation of health care programs. Oxford, Oxord University Press, pp. 1-38, 1987.

4. Naslund, M., Bay-Nielsen, H., Holtgrewe, L., Homma, Y. and Melchior, H.: The economics of benign prostatic hyperplasia. In: Benign Prostatic Hyperplasia, Proceedings of the 5th International Consultation on Benign Prostatic Hyperplasia. Edited by C. Chatelain, L. Denis, K.T. Foo, S. Hkouty and J. McConnell, edition 2001, Plymouth, UK, Plymbridge Distributors, pp. 69-78, 2001.

5. Noble, S.M., Coast, J., Brookes, S., Neal, D.E., Abrams, P., Peters, T.J., et al.: Transurethral prostate resection, noncontact laser therapy or conservative management in men with symptoms of benign prostatic enlargement? An economic evaluation. J. Urol. 168: 2476-2482, 2002.

6. Fraundorfer, M.F., Gilling, P.J., Kennett, K.M. and Dunton, N.G.: Holmium laser resection of the prostate is more cost effective than transurethral resection of the prostate: results of a randomized prospective study. Urol., 57: 454-458, 2001.

7. Keoghane, S.R., Lawrence, K.C., Gray, A.M., Doll, H.A., Hancock, A.M., Turner, K. et al: A double-blind randomized controlled trial and economic evaluation of transurethral resection vs contact laser vaporization for benign prostatic enlargement: a 3-year follow-up. Br. J. Urol., 85: 74-78, 2000.

8. Keoghane, S.R., Lawrence, K.C., Gray, A.M., Chappel, D.B., Hancock, A.M. and Cranston, D.W.: The Oxford laser prostate trial: economic issues surrounding contact laser prostatectomy. Br. J. Urol., 77: 386-390, 1996.

9. Mueller, E.J.: Contact laser vaporization of the prostate: one surgeon’s experience with 50 consecutive cases. Tech. Urol., 2: 136-141, 1996.

10. Albertsen, P.C., Pellissier, J.M., Lowe, F.C., Girman, C.J. and Roehrborn, C.G.: Economic analysis of finasteride: a model-based approach using data from the proscar® long-term efficacy and safety study. Clin. Ther. 21: 1006-1024, 1999.

11. Blute, M., Ackerman, S.J., Rein, A.L., Beusterien, K., Sullivan, E.M., Tanio, C.P., et al.: Cost effectiveness of microwave thermotherapy in patients with benign prostatic hyperplasia: part II-results. Urol. 56: 981-987, 2000.

12. Nørby, B., Nielsen, H.V. and Fromodt-Møller, P.C.: Cost-effectiveness of new treatments for benign prostatic hyperplasia: results of a randomized trial comparing the short-time cost-effectiveness of transurethral interstitial laser coagulation of the prostate, transurethral microwave therapy and standard transurethral resection of the prostate. Scand. J. Urol. Nephrol., 36: 286-295, 2002.

13. Van Melick, H.H., van Venrooij, G.E., Eckhardt, M.D. and Boon, T.A.: A randomized controlled trial comparing transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia: urodynamic effects. J. Urol. 168: 1058-1062, 2002.

14. Van Melick, H.H., van Venrooij, G.E., Eckhardt, M.D. and Boon, T.A.: A randomized controlled trial comparing transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia: analysis of subjective changes, morbidity and mortality. J. Urol., 169: 1411-1416, 2003.

15. Van Melick, H.H., van Venrooij, G.E., Eckhardt, M.D. and Boon, T.A.: Long-term follow-up after transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia. Urol. accepted.

16. Barry, M.J., Fowler jr., F.J., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L, Mebust, W.K., et al : The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J. Urol., 148: 1549-1557, 1992.

17. Barry, M.J., Fowler jr., F.J., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L and Mebust, W.K.: Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of the American Urological Association. Med. Care, 4 suppl., 33: AS145-155, 1995.

CHAPTER 8

Laser prostatectomy

in patients on anticoagulant therapy

or with bleeding disorders

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Abstract

Introduction: Bleeding disorders or the use of anticoagulant medication are contraindications for transurethral prostate resection (TURP) in men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH). Laser prostatectomy has proven to be adequate surgical therapy with less blood loss than TURP.

Materials and methods: A prospective, controlled study was done in patients at high-risk (HR) with LUTS suggestive of BPH. They were treated with contact laser prostatectomy (CLP) or the combination of CLP with visual laser ablation prostatectomy (VLAP). High-risk was defined as having bleeding disorders or using anticoagulants. As a control, men at normal-risk (NR) with LUTS suggestive of BPH were treated with CLP. Patients completed validated questionnaires and underwent urodynamics at baseline and six months postoperatively.

Results: A total of 75 patients were included, namely 19 in the HR-CLP group, 11 in the HR-CLP-VLAP group and 45 in the NR-CLP group. Obstruction relief and symptomatic and subjective improvement were equal in all three groups. Effective capacity (maximum cystometric capacity minus post-void residual volume) also improved significantly in all groups except the HR-CLP group. Maximum uroflow improved in all groups but not significantly in the HR-CLP group.
intra and postoperatively complications were slightly higher in HR patients. However, blood transfusion was never necessary and there was no mortality.

Conclusions: CLP and especially CLP-VLAP perform nearly as well in high-risk patients compared with CLP in those at normal-risk. These procedures are safe for patients at high-risk with LUTS suggestive of BPH.

Introduction

Men presenting with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) are treated in several ways depending on the severity of their symptoms, bother and their preference. For several decades, transurethral resection of the prostate (TURP) has been the gold standard when surgical treatment was necessary. Nevertheless, this surgical procedure is associated with an intra-operative morbidity, especially bleeding and perforation, varying from 6.9 to14%[1-4]. Morbidity within 30 days Postoperatively varies from 9.5% to 18%[1-4] and consists mainly of bleeding. This makes TURP in men on anticoagulant therapy or with bleeding disorders contraindicated. Temporarily stopping anticoagulant drugs, e.g. in patients with pulmonary embolism, chronic atrial fibrillation, cardiovascular incidents or prosthetic heart valves increases the risk of thrombo-embolic processes. If there is an important indication for surgical intervention, the most commonly used procedure is stopping anticoagulants several days preoperatively and using heparin intravenously per-operatively[5]. The much shorter half-life of heparin makes it possible to stop it only for a few hours peri-operatively. Postoperatively, oral anticoagulant therapy can be resumed. This procedure only partially reduces the risk for thrombo-embolic processes. In addition, there is already an increased risk of 6.8%-10% for deep venous thrombosis in normal patients undergoing TURP[6].

In the past, some authors concluded that it is possible to perform TURP while continuing oral anticoagulant therapy[7], without temporarily stopping intravenous heparin[8] or with heparin subcutaneously[9,10]. These studies, however, were only performed in very small populations and few clinicians follow these regimens.

The introduction of laser prostatectomy in various modalities offered a new perspective for these patients. All laser types have the ability to coagulate and minimize bleeding. Previously, we demonstrated that contact laser prostatectomy (CLP) performs urodynamically, symptomatically and subjectively equal to the gold standard TURP[11,12]. Regarding intra-operative and post-operative complications, there was significantly less blood loss in men treated with CLP.

Several other authors reported good results for all types of laser therapy in patients on anticoagulant therapy or with bleeding disorders, however, the literature is scarce and is often only case reports[13-17].

We analyzed the results of CLP and a combination of CLP with visual laser ablation prostatectomy (VLAP). Patients were men with LUTS suggestive of BPH that also had various bleeding disorders, or were using oral anticoagulants or thrombocyte aggregation inhibitors.

Materials and methods

A prospective, controlled study was conducted between 1994 and 2002 at our clinic. High-risk (HR) patients were defined as patients using anticoagulants (acenocoumarol or fenprocoumon, both coumarine derivatives), using thrombocyte aggregation inhibitors (carbasalate calcium) or having various bleeding disorders. These patients were selected in, or referred to our outpatient department. HR patients with LUTS suggestive of BPH were included if withdrawal of anticoagulants created unacceptable risks according to their cardiologist. Conservative treatment had to fail or they had to be in urinary retention. Patients on coumarine derivatives with an INR (international normalized ratio) <1.2 directly preoperatively were excluded.

Patients had to be urodynamically equivocal or obstructed (Schäfer grade ≥2) and their prostate volume had to be between 20 and 65 ml. Patients with any of the exclusion criteria (except bleeding disorders or anticoagulants) of the International Consensus Committee on BPH were excluded from analysis[18], e.g. prostate cancer or urolithiasis. If patients fulfilled the inclusion and exclusion criteria and signed informed consent, they were treated with hybrid therapy (a combination of CLP and VLAP) or CLP. Hybrid therapy was performed from 1994 to 1996 and CLP from 1996 to 2002.

All patients had thorough histories taken and underwent digital rectal examination, transrectal ultrasonography, urodynamics, free uroflowmetry, post-void residual urine volume estimation, urinalysis and blood analysis including haemoglobin and coagulation parameters. Symptomatic and subjective parameters were measured by questionnaires validated by the American Urological Association (AUA). Patients completed the International Prostate Symptom Score Index (IPSS)[19], the Symptom Problem Index (SPI or bother score index)[20], the BPH Impact Index (BII)[20] and the Quality of Life question (QoL)[19]. These questionnaires were completed before surgery and 6 months Postoperatively. Urodynamics consisted of filling cystometry, pressure-flow studies and free uroflowmetry. These were performed preoperatively and six months Postoperatively. Post-void urine volume was estimated by catheterization. Effective bladder capacity was defined as the maximum cystometric capacity minus the post-void residual volume. Uroflowmetric results were only included if patients voided over 150 ml. Complications were registered both intra-operatively and Postoperatively for up to twelve months.

CLP was performed with an SLT Nd:YAG laser with an MTRL 10, 6x5 mm, sapphire tipped probe (Surgical Laser Technologies, Oaks, Pennsylvania). It uses laser light to heat a rounded black tip. Upon contact with prostatic tissue this causes direct tissue ablation by vaporization and leaves behind a coagulated layer. VLAP was performed with a Nd:YAG laser with a right angle fibre delivery system (Urolase CR Bard Inc.,

Covington, Georgia). This type of free beam laser deflects laser light at a right angle to necrotize, vaporize and coagulate prostatic tissue. A gold-plated alloy dish reflector tip fixed to the distal end ensured 90º deflection of laser light into the prostatic tissue. Laser treatment was applied to four positions in the lateral lobes for prostate volumes below 40 ml and to eight positions for larger prostates. At each site, laser light was applied for 90 seconds at a setting of 40 watts. CLP was used after VLAP to vaporize and coagulate the bladder neck and, if present, the median prostatic lobe.
All patients were operated while using intravenous antibiotics and the surgeries were always performed by the same urologist. A three-way catheter was left in place, Postoperatively.
Parallel to the present study, a partially overlapping randomized controlled trial[11,12] was conducted comparing TURP, electrovaporization and CLP in men with LUTS suggestive of BPH. Inclusion and exclusion criteria were similar except for the bleeding status of the patients. These normal-risk (NR) patients treated with CLP were used as a control.
Statistical analyses were performed with ANOVA, Kruskal-Wallis, Chi-square test, Student-t test, Mann-Whitney U test and Wilcoxon signed-ranks test. The Kolmogorov-Smirnov test was used to analyze the normal distribution of parameters. Significance was set at $p=0.05$. Data are presented as means ± standard deviations, unless otherwise mentioned.

Results

Between 1994 and 2002, thirty high-risk (HR) patients were treated by laser prostatectomy: 11 by hybrid therapy (VLAP-CLP) and 19 by CLP. From 1996 to 2002, forty-five normal-risk (NR) patients were treated with CLP[11,12].
Table 1 lists the high-risk characteristics for the two HR groups. In the HR-CLP group, 11 patients used coumarine derivatives, 3 patients used thrombocyte aggregation inhibitors and 5 patients suffered from bleeding disorders. From the latter subgroup; 2 had haemophilia, 1 a uraemic thrombopathy, 1 a myelodysplastic syndrome and 1 a coagulation disorder of unknown origin. In the HR-Hybrid group, 8 patients used coumarine derivatives and 3 suffered from bleeding disorders of unknown origin.
Table 2 lists the baseline characteristics of the HR patients and the NR-CLP patients. There were no significant differences at baseline between the groups.
In table 3 the baseline values are presented together with the 6 months post-operative results. These values are also graphically represented in figures 1 to 4.
Within the different groups there were always significant changes, with the following exceptions: maximum flow and effective capacity in the HR-CLP group; bother index,

Table 1 High-risk characteristics. In 1a only the main reason for using anti-coagulant therapy is presented.

	HR-CLP n=19	HR-Hybrid n=11
1a: Anti-coagulants or thrombocyte aggregation inhibitors		
Prosthetic heart valve(s)	2	2
Vascular prosthesis	1	0
Chronic atrial fibrillation	3 (5)[1]	1 (3)[1]
Aneurysma cordis	1	1
Myocardial infarction	2	1
Pacemaker	1	0
Deep venous thrombosis	0	1
Pulmonary embolism	1	1
Cerebro-vascular accident	3	1
1b: Bleeding disorders		
Haemophilia	2	0
Other bleeding disorders	3	3

1. The number between brackets shows the total number of men with atrial fibrillation. This number includes men with atrial fibrillation in whom their was another main reason to start anticoagulant therapy.

Table 2 General, urodynamic and symptomatic characteristics of high-risk (HR) patients and normal-risk (NR) controls preoperatively. Data presented as means ± standard deviation.

	HR-Hybrid	HR-CLP	NR-CLP	p level between[1]
Number of patients	11	19	45	-
Age (years)	72 ± 5	70 ± 7	67 ± 9	0.2
Prostate volume (ml)	37 ± 14	35 ± 17	37 ± 11	0.9
Obstruction grade (Schäfer)	3.1 ± 1.4	3.3 ± 1.0	3.2 ± 1.2	0.9
Maximum flow (ml/sec)	11.8 ± 3.1	12.5 ± 1.8	11.5 ± 4.1	0.7
Effective capacity (ml)	272 ± 209	369 ± 167	302 ± 133	0.3
Symptom Score Index	21.1 ± 5.0	18.9 ± 6.5	18.9 ± 6.8	0.5
Symptom Problem Index	11.9 ± 5.6	11.7 ± 7.3	12.5 ± 7.8	0.4
BPH Impact Index	12.8 ± 4.3	10.3 ± 3.5	9.5 ± 4.0	0.07
Quality of Life	3.9 ± 2.1	4.0 ± 1.3	3.7 ± 1.6	0.8

1. ANOVA and chi-square test used.

Table 3 Urodynamic, symptomatic and subjective changes postoperatively of high-risk (HR) patients and normal-risk (NR) controls. Data presented as means ± standard deviation.

	Pretreatment	6 months Posttreatment	Change as ratio and percent [1]	p level within	p level between
Schäfer obstruction grade					
HR-Hybrid	3.1 ± 1.4	1.2 ± 1.2	0.39 (-61%)	<0.01	0.7
HR-CLP	3.3 ± 1.0	1.1 ± 0.4	0.33 (-67%)	<0.01	
NR-CLP	3.2 ± 1.2	1.0 ± 1.0	0.31 (-69%)	<0.001	
Maximum Flow (ml/s)					
HR-Hybrid	11.8 ± 3.1	22.6 ± 9.9	1.92 (+92%)	0.01	0.01 (0.01 between HR-CLP and NR-CLP)
HR-CLP	12.5 ± 1.8	17.8 ± 5.5	1.42 (+42%)	0.08	
NR-CLP	11.5 ± 4.1	23.8 ± 7.2	2.07 (+107%)	<0.001	
Effective capacity (ml)					
HR-Hybrid	272 ± 209	417 ± 209	1.53 (+53%)	0.02	0.08
HR-CLP	369 ± 167	357 ± 173	0.97 (-3%)	0.7	
NR-CLP	302 ± 133	437 ± 120	1.45 (+45%)	<0.001	
Symptom Score Index					
HR-Hybrid	21.1 ± 5.0	8.0 ± 7.8	0.38 (-62%)	0.04	0.7
HR-CLP	18.9 ± 6.5	7.6 ± 4.5	0.40 (-60%)	0.01	
NR-CLP	18.9 ± 6.8	6.6 ± 5.8	0.35 (-65%)	<0.001	
Bother Score Index					
HR-Hybrid	11.9 ± 5.6	3.8 ± 5.6	0.32 (-68%)	0.09	0.3
HR-CLP	11.7 ± 7.3	3.6 ± 4.3	0.31 (-69%)	0.04	
NR-CLP	12.5 ± 7.8	2.8 ± 4.4	0.22 (-78%)	<0.001	
BPH Impact Index					
HR-Hybrid	12.8 ± 4.3	5.3 ± 6.8	0.41 (-59%)	0.1	0.09
HR-CLP	10.3 ± 3.5	2.5 ± 2.1	0.24 (-76%)	0.01	
NR-CLP	9.5 ± 4.0	3.2 ± 3.5	0.34 (-66%)	<0.001	
Quality of Life					
HR-Hybrid	3.9 ± 2.1	2.2 ± 2.3	0.56 (-44%)	0.3	0.5
HR-CLP	4.0 ± 1.3	1.6 ± 1.4	0.40 (-60%)	0.03	
NR-CLP	3.7 ± 1.6	1.1 ± 1.1	0.30 (-70%)	<0.001	

1. Ratio = postvalue/ prevalue, and percent change = {(prevalue – postvalue)/ prevalue} * 100%

Table 4 Perioperative parameters. Data presented as means ± standard deviation.

	HR-Hybrid	HR-CLP	NR-CLP	p level between[c]
Operation time (min)	50 ± 15	58 ± 16	58 ± 11	0.6
Blood loss intraoperatively [a]	0.7 ± 0.8	0.5 ± 0.7	0.6 ± 0.7	0.8
Change in Hb (mmol/l) [b]	8.9 ± 1.2 → 8.5 ± 0.9 p = <0.01	8.5 ± 0.7 → 8.0 ± 1.0 p = 0.03	9.0 ± 0.9 → 8.8 ± 0.8 p = 0.3	0.06
Irrigation fluid (l)	16 ± 6	16 ± 5	18 ± 4	0.2
Drainage time (days)	7.3 ± 6.6 median: 6	2.6 ± 1.3 median: 2	2.8 ± 3.1 median: 2	<0.01
Postoperative hospital stay (days).	7.0 ± 1.1	6.1 ± 2.3	3.8 ± 1.3	<0.001
INR direct preoperatively	2.2 ± 1.2	2.1 ± 0.9	-	0.7
Energy (kJ)	51 ± 17	58 ± 24	48 ± 17	0.2

1. Blood loss: 0=none, 1=moderate and 2=severe. Visual estimation intra-operatively by urologist.
2. Hb = haemoglobin: pre → post-operative value, including significance of decrease within group (Student-t test).
3. Operation time, change in Hb, irrigation and hospital stay with ANOVA; blood loss, drainage time and energy with Kruskal-Wallis test. INR with Student's t test.

BPH impact index and Quality of Life in the HR-Hybrid group. All changes were significant in the NR controls. Statistical analysis of the relative changes between the groups did not show any significant differences, except for maximum free flow. Further analysis demonstrated a significant difference (p=0.01) between NR-CLP and HR-CLP patients. Urodynamically there was always desobstruction in both HR groups. Postoperatively in the HR-CLP group, all patients had Schäfer grade 1 except one patient with grade 2. In the HR-Hybrid group there was one patient with Schäfer grade 3 Postoperatively (grade 4 at baseline); the remaining patients had Schäfer grade <2. Forty-one out of 45 NR-CLP patients had Schäfer grade <2 Postoperatively[11].

Peri-operative data are presented in table 4. Mean operation time was less than one hour in all groups and no significant differences were observed. There were also no significant differences in use of irrigation fluid or laser energy . INR was estimated in patients on coumarine derivatives and did not differ significantly between the HR groups. Visually estimated blood loss intra-operatively also showed no significant differences between the groups. Within the HR groups there was a small, but significant, decrease in haemoglobin. No significant change was observed in the NR controls. Analysis of this haemoglobin change between the three groups did not show a significant difference, although there was a trend in favour of the NR controls

Table 5 Number of intraoperative complications.

	HR-Hybrid	HR-CLP	NR-CLP
Capsule perforation	0	0	2
Bleeding, making electrocoagulation necessary	1	3 [b]	2
Bleeding, making TURP necessary	0	0	3
False passage	0	0	1 [1]
Technical failure	0	0	3
Use of TURP because of tissue debris	3-5	4 [2]	3

1. False passage made during first introduction of the scope
2. One patient required TURP for tissue debris and electrocoagulation for bleeding, which were counted seperately.

Table 6 Postoperative morbidity and mortality within 12 months (without urinary tract infections).

	HR-Hybrid n=11	HR-CLP n=19	NR-CLP n=45
Bleeding requiring transfusion	0	0	0
Clot retention	1	3	2
Urinary retention	1	1	5
Reoperation (TURP)	0	1	1
Reoperation (electrocoagulation)	1	0	0
Urethral strictures	0	1	2
Bleeding requiring rehospitalization and irrigation	1	2 [1]	0
Other	0	0	1 epididymitis
Mortality	0	0	0

1. In one patient INR was >5 and vitamin K was used to correct coagulation status next to irrigation.

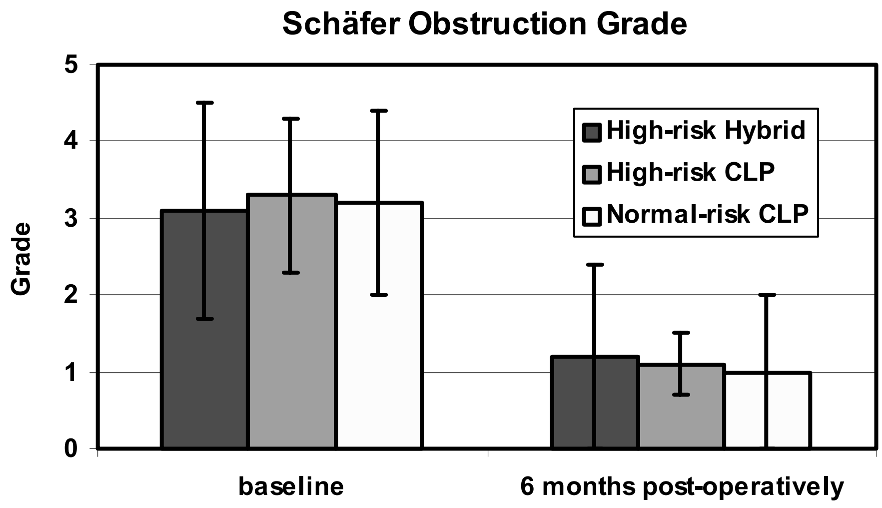

Figure 1 Graphic representation of the Schäfer obstruction grade in the three different groups at baseline and six months postoperatively. Data presented as means ± standard deviations.

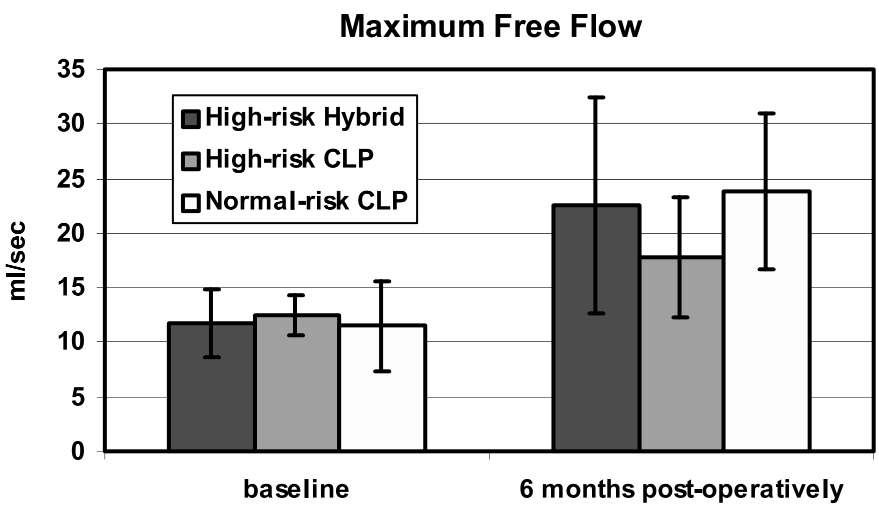

Figure 2 Graphic representation of the maximum free flow (in ml/sec.) in the three different groups at baseline and six months postoperatively. Data presented as means ± standard deviations.

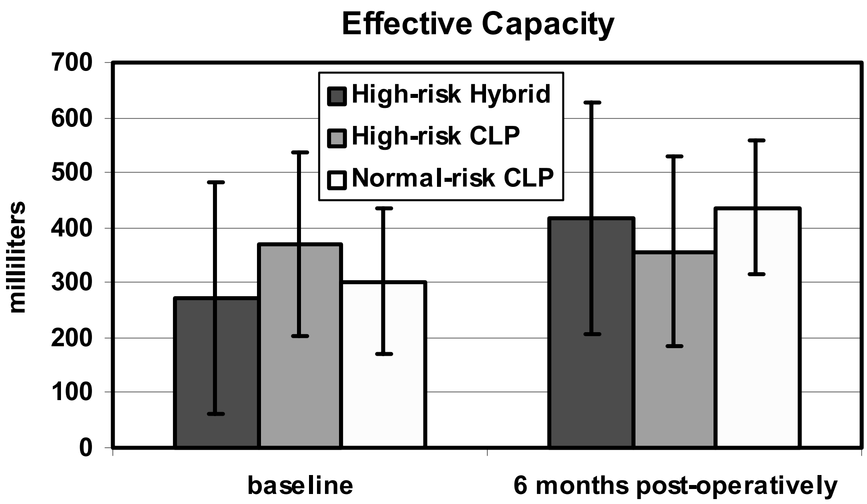

Figure 3 Graphic representation of the effective capacity in the three different groups at baseline and six months postoperatively. Effective capacity is defined as the maximum cystometric capacity minus the post-void residual volume. Data presented as means ± standard deviations.

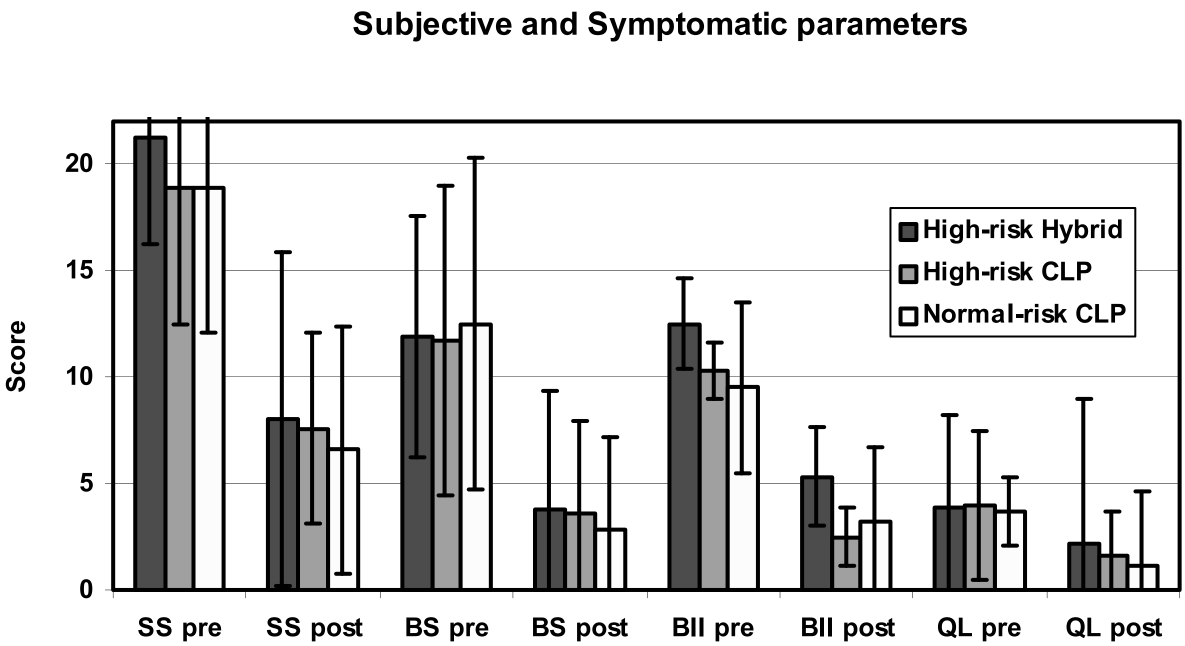

Figure 4 Graphic representation of subjective and symptomatic parameters in the three different groups at baseline and six months postoperatively. SS: symptom score index, BS: bother score index or symptom problem index, BII: BPH impact index, and QL: Quality of Life. Data presented as means ± standard deviations.

(p=0.06). No significant difference for drainage time was demonstrated between the CLP groups, but there was an obvious and significant difference between these groups and the HR-Hybrid group. Hospital stay was significantly longer in the HR groups compared to the control patients.
Table 5 presents the intra-operative complications. In all groups, electroresection was sometimes performed because of tissue debris. Electro-coagulation was most used in the HR-CLP group. Comparison to the HR-Hybrid group is impossible because of small numbers. Post-operative complications are described in table 6.
More complications were observed in the HR patients. Blood transfusions were not necessary in any of the groups, nor was there any mortality.

Discussion

In the early nineties, many new treatment modalities were developed to overcome the relatively high morbidity and mortality rates of TURP[1-4], including the introduction of several laser treatments. Their good coagulative characteristics make them theoretically ideal to perform prostatectomies in high-risk patients. A randomized controlled trial at our department demonstrated that CLP matched the symptomatic, subjective and urodynamic improvements of TURP but with less blood loss[11,12]. Intra-operative and post-operative complications were also comparable.
The use of electroresection to remove tissue debris was only used in the first years of this study in very specific situations that were not foreseen, and only to remove a few small tissue particles. The clinical significance is very doubtful and we abandoned this practice in later years.
Several studies on HR patients with different laser types have been conducted in the past. Polepalle[17] conducted an interstitial laser therapy pilot study in an ambulatory setting on 8 men with LUTS while continuing warfarin anticoagulant therapy. No patients required hospitalization, blood transfusion or irrigation. Maximum uroflow and symptom score improved fairly. Bolton[16] presented a VLAP study with ten symptomatic BPH patients and continuing warfarin peri-operatively. There were no significant peri-operative complications, with one patient needing irrigation because of clot retention. Maximum uroflow improved from 9 to15 ml/sec, post-void residual volume decreased from 485 to 105 ml and symptom score decreased from 21 to 7. Kingston[15] also reported a VLAP study in 20 men with continuous warfarin therapy and 2 men with coagulation disorders (idiopathic thrombocytopenia and leukaemia). Mean prostate volume was with 56 ml larger than in the present study. After six months, symptom score improved from 21 to 7, maximum uroflow from 9.8 ml/sec to 12.0 ml/sec and post-void-residual urine from 80 ml to 48 ml. Three patients required post-operative blood transfusions and one of these patients sustained a cerebrovascular accident because of reversal of anticoagulant therapy and TURP.

One patient developed epididymo-orchitis and one required rehospitalization because of haematuria.
Until now, two studies with CLP in HR patients have been conducted. Keoghane[13] presented three cases of men continuing warfarin therapy with mixed results. One patient was readmitted Postoperatively because of minor secondary haemorrhage, one patient recovered with good results and one patient (prostate volume 112 ml) suffered from haemorrhage directly Postoperatively, requiring 5 units of blood. Mueller[14] reported six cases of men treated with CLP who continued warfarin peri-operatively. In all men, catheter removal and hospital discharge occurred on day one. None developed any significant bleeding peri-operatively and all had excellent relief of their obstructive symptoms.
To the best of our knowledge, the present study is the first to perform urodynamics in all patients and to make use of a control group. The latter makes it possible to see if HR patients are operated less efficiently because of fear of bleeding. The first 11 HR patients were treated with CLP-VLAP (Hybrid), but from 1996 HR patients were treated with CLP only. The main reasons for this change were that CLP is easier to perform and gives similar results to hybrid therapy. Because of this, CLP was used in a second trial with normal risk patients, increasing our experience significantly.
All groups were statistically compared, although patients in the present study were not randomized. However, inclusion and exclusion criteria are equal and baseline values are also very similar, except for their bleeding status.
A good desobstruction was achieved in all groups. Nevertheless, there was only a minor increase in maximum flow in the HR-CLP group (p=0.08). This can be partially explained by a decrease in contractility within this group (2.6 to 2.0: p=0.4). There was a slight increase in contractility in the HR-Hybrid group (2.9 to 3.3: p=0.3). The same explanation may be apply to the effective capacity: a large increase in the HR-Hybrid group and the control group, but almost no change in the HR-CLP group. However, because of a large variation within the groups there was no significant difference in the change between the groups. There were no significant differences in the symptomatic and subjective improvements between the groups. Within the groups, all improvements were significant except for the HR-Hybrid group. In this group, only the symptom score index improved significantly (p=0.04). Change in haemoglobin did not differ significantly between the groups, though there was a trend in favour of the control group (p=0.06). Haemoglobin decrease was not significant in the control group and was small (0.4 mmol/l), but significant, within the HR groups. The clinical relevance of these changes is small, demonstrating intra-operative safety. Drainage times were comparable between the two CLP groups and were significantly shorter than in the HR-Hybrid group. This difference can be explained by directly obtained desobstruction in CLP caused by vaporization. VLAP causes more tissue necrosis and requires a longer catheterization period. Hospital stay did not differ significantly between the HR groups. HR-CLP patients were hospitalized for

longer observation periods as a precautionary measure. Retrospectively, this regimen may have been too careful since only 3 out of 19 patients had clot retention and these were always in men with gross haematuria after catheter removal. Intra-operative and post-operative complications were not compared statistically because of small numbers. There may be slightly more intra-operative bleedings and post-operative clot retentions in the HR-CLP group. Although some other studies reported blood transfusions, these were never necessary in the present study.

Conclusions

The use of CLP and the combination CLP with VLAP in high-risk patients with LUTS suggestive of BPH can safely be performed. Compared to CLP in normal risk patients, there are only small differences in symptomatic and subjective improvements. Urodynamic desobstruction was equal in all groups, although HR-CLP patients showed a smaller increase in maximum flow and an unchanged effective capacity. Intra-operative and post-operative complications were almost equal between all groups. Blood transfusion was never necessary nor was there any mortality.

References

1. Horninger, W., Unterlechner, H., Strasser, H. and Bartsch, G.: Transurethral prostatectomy: mortality and morbidity. Prostate, 28: 195, 1996.

2. Mebust, W.K., Holtgrewe, H.L., Cockett, A.T., Peters, P.C. and Writing Committee: Transurethral prostatectomy: immediate and post-operative complications. A cooperative study of 13 participating institutions evaluating 3885 patients. J. Urol., 141: 243, 1989.

3. Uchida, T., Ohori, M., Soh, S., Sato, T., Iwamura, M., Oa, T. et al: Factors influencing morbidity in patients undergoing transurethral resection of the prostate. Urol., 53: 98, 1999.

4. Doll, H.A., Black, N.A., McPherson, K., Flood, A.B., Williams, G.B. and Smith, J.C.: Mortality, morbidity and complications following transurethral resection of the prostate for benign prostatic hypertrophy. J. Urol., 147: 1566, 1992.

5. Chakravarti, A. and MacDermott, S.: Transurethral resection of the prostate in the anticoagulated patient: BJU 81: 520, 1998.

6. Hedlund, P.O.: Postoperative venous thrombosis in benign prostatic disease. A study of 316 patients using the 125 I-Fibrinogen uptake test. Sand. J. Urol. Nephrol. (Suppl. 27): 1, 1975.

7. Parr, N.J., Loh, C.S. and Desmond, A.D.: Transurethral resection of the prostate and bladder tumour without withdrawal of warfarin therapy. BJU 64: 623, 1989.

8. Tscholl, R., Straub, W. and Zingg, E.: Electroresection of the prostate in patients treated with heparin. J. Urol., 124: 221, 1980.

9. Wilson, R.G., Smith, D., Paton, G. Gollock, J.M. and Bremner, D.N.: Prophylactic subcutaneous heparin does not increase operative blood loss in transurethral resection of the prostate. BJU 62: 246, 1988.

10. Sleight, M.W.: The effect of prophylactic subcutaneous heparin on blood loss during and after transurethral prostatectomy. BJU 54: 164, 1982.

11. Van Melick, H.H., van Venrooij, G.E., Eckhardt, M.D. and Boon, T.A.: A randomized controlled trial comparing transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia: urodynamic effects. J. Urol., 168: 1058, 2002.

12. Van Melick, H.H., van Venrooij, G.E., Eckhardt, M.D. and Boon, T.A.: A randomized controlled trial comparing transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia: analysis of subjective changes, morbidity and mortality. J. Urol., 169: 1411, 2003.

13. Keoghane, S.R. and Cranston, D.W.: Contact laser prostatectomy in anti-coagulated patients: mixed results. BJU 77: 613, 1996.

14. Mueller, E.J.: Contact laser vaporization of the prostate in patients on chronic anticoagulant therapy. Tech. Urol. 4: 156, 1998.

15. Kingston, T.E., Nonnenmacher, A.K., Crowe, H., Costello, A.J. and Street, A.: Further evaluation of transurethral laser ablation of the prostate in patients treated with anticoagulated therapy. Aust. N.Z. J. Surg. 65: 40, 1995.

16. Bolton, D.M. and Costello, A.J.: Management of benign prostatic hyperplasia by transurethral laser ablation in patients treated with warfarin anticoagulation. J. Urol. 151: 79, 1994.

17. Polepalle, S. and Monga, M.: Interstitial laser therapy for benign prostatic hyperplasia in the anticoagulant patient. Tech. Urol. 7: 285, 2001.

18. Chatelain, C., Denis, L., Foo, K.T., Khoury, S., McConnell, J., Abrams, P. et al: Recommendations of the international scientific committee: Evaluation and treatment of lower urinary tract symptoms (LUTS) in older men. In: Benign Prostatic Hyperplasia, 5th International Consultation on BPH. edition 2001, Plymouth, UK, Plymbridge Distributors, pp. 519-534, 2001.

19. Barry, M.J., Fowler jr., F.J., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L., Mebust, W.K. et al: The American Urological Association symptom index for benign prostatic hyperplasia. J. Urol., 148: 1549, 1992.

20. Barry, M.J., Fowler jr., F.J., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L. and Mebust, W.K.: Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of the American Urological Association. Med. Care, Suppl., 33: AS145, 1995.

CHAPTER 9

General Discussion, Conclusions and

Future Perspectives

GENERAL DISCUSSION

Chapter 1 gives an introduction to several aspects that are related to the prostate. It describes the anatomy and physiology of the prostate and the etiology of benign prostatic pathology with its natural history. The term LUTS (lower urinary tract symptoms) is described together with the possibilities to quantify these symptoms and their bothersomeness. This term refers to the location of several urinary problems, instead of the old term 'prostatism', which refers to an incorrect etiology. It is clearly stated that many factors can cause LUTS. The exact share of the different (benign) pathological states is thus far not completely solved. Benign pathological states can be categorized into a histological diagnosis, a mechanical diagnosis or a volumetric diagnosis, respectively BPH (Benign Prostatic Hyperplasia), BPO (Benign Prostatic Obstruction) and BPE (Benign Prostatic Enlargement).

The term BPH is used in the title of this thesis, merely because it is such a generally accepted term. The adjective 'clinical' is necessary to indicate that LUTS are involved. All patients that were included in the studies of the following chapters are described as having 'LUTS associated with BPH' or 'LUTS suggestive of BPH'. One can argue the accuracy of these descriptions, because most patients have never been histologically diagnosed. However, these descriptions are often used in literature because of the lack of accurate terminology.

Chapters 2 and 3 deal with urodynamics in the context of performing the gold standard, TURP. In chapter 2, men with LUTS associated with BPH who were treated by TURP were studied. Ninetythree patients could be evaluated after 6 months of the 132 men that were included. Of these 93 men, 32 men were preoperatively unobstructed (Schäfer grade 1 or 2) and the remaining 61 were obstructed (Schäfer grade ≥3). Symptomatic improvements were significantly related with a decrease in bladder outlet obstruction. Nevertheless, also the unobstructed patients benefited from TURP. Looking at all patients, there was a 45% increase in effective capacity, which contributed to a significant improvement in I-PSS, SPI, QoL and BII. Of the patients with a preoperative stable bladder, 90% remained stable postoperatively. In those with a preoperative unstable bladder, 50% became stable postoperatively. However, which bladder becomes stable could not be predicted preoperatively from subjective or objective parameters.

The finding in chapter 2 that patients who were not obstructed or were equivocal showed a significant and clinical relevant increase in both subjective and objective findings, was the reason to analyze this topic more intensively in chapter 3. It appeared that the quantified reduction of symptoms and bother in the unobstructed and equivocal men were about 70% of those reductions in obstructed men. In the equivocal men and even in the unobstructed men a significant reduction with 40% of the urethral resistance occurred. It is demonstrated that for unobstructed or equivocal men with considerable LUTS and BPE, who opt for resection, who do not respond to medical therapy and/or in whom adverse effects are associated with treatment discontinuation, prostate resection appeared to be a good treatment alternative. The presence or absence of urethral obstruction should not be the decisive factor in treatment choice, and absence of obstruction should not be an exclusion criterion for transurethral prostate resection.

The expanding armamentarium of minimally invasive surgical modalities over the last decade, has not dethroned TURP as being the gold standard. This raises some questions. How is it possible that all these new technologies cannot surpass or even match a modality that is half a century old? And when exactly is a new treatment more successful than an older one? The answers are probably hard to find. Each (surgical) treatment strategy should be evaluated in a context of objective and subjective treatment results, complications and side-effects. And possibly more aspects are of importance in the acceptance of a new modality: are the surgical characteristics interestingly to perform, what is the cost-effectiveness ratio, are long-term results available, have there been multicenter, randomized, controlled trials and what is the influence of the manufacturers? Many characteristics are important and it takes a lot of time and effort of many scientists and clinicians to correctly introduce a new modality. The scientific standards are high nowadays and demand that each new surgical modality is compared to the gold standard (TURP) in a randomized setting.

In reality, the process of introducing a new modality is influenced by many factors, like individual (scientific) ambition and financial fundings. In this way, the process does not always comply with the stringent methodological rules. A long time period can elapse from the first pilot studies presenting the feasibility of a technique to long-term results from large randomized controlled studies. Sometimes this process is not even completed, because another new technique deserves more attention. It can be of more interest to publish about another new technique than to perform all the work involved in long-term follow-up of patients treated with an already known modality. A regrettable event from a scientifically point of view.

The history of the introduction of TURP presents a perfect example of a process that did not follow the solid methodological rules of medical science. New developments improved the quality of endoscopic surgery and slowly made TURP the most popular surgical modality. Unfortunately, its success caused a historical, scientific gap, that will never be filled. It became normal to perform a TURP instead of an open prostatectomy, without waiting for a decent comparison between these two surgical modalities. Besides one small randomized study, there has been no comparison between open prostatectomy and TURP. Nowadays, it is considered unethical to perform a randomized trial comparing these two techniques. TURP became the gold standard over several decades, and it is still considered to be so at this moment. Many of today's urologists have been educated with TURP as gold standard and it will cost a lot of effort to change this regimen. It is to be hoped, that all new techniques that demonstrated to be feasible alternatives, obtain their deserved objective, scientific attention. Ultimately, it is in the interest of the patient's quality of life that new medical technologies are developed, tested and introduced.

In our clinic, a randomized, controlled trial was performed from 1996 to 2002 comparing two minimally invasive surgical modalities to the gold standard TURP. These new modalities were contact laser prostatectomy and electrovaporization, both introduced in urology about ten years ago. The number of randomized controlled trials however is limited and several aspects, like costs, have almost never been studied. Included were men over 45 years of age with LUTS associated with BPH. All patients underwent history taking, digital rectal examination, transrectal ultrasonography, urodynamic evaluation, free flowmetry, post-void residual volume estimation, urinalysis and blood analysis. Patients had to be urodynamically equivocal or obstructed (Schäfer grade ≥2). Their prostate volume had to be between 20 and 65 ml. Patients with any of the exclusion criteria of the International Consensus Committee on BPH were excluded from analysis. The results of this randomized controlled trial are presented in chapters 4 to 7.

Chapter 4 compares the urodynamic results of TURP, contact laser prostatectomy (CLP) and electrovaporization. The baseline characteristics of the three groups are very similar. The number of included patients complies with the calculated group sizes. A total of 50, 45 and 46 men were randomized for TURP, CLP and electrovaporization respectively. Six months postoperatively we were able to evaluate 70% of the initially examined patients. There were no statistically significant differences in the changes between the different modalities for all urodynamic parameters. Detrusor pressure at maximum urinary flow decreased by half. There was no significant change in bladder contractility. The Schäfer discrete obstruction grade and the continuous urethral resistance factor decreased significantly. After TURP, 94% was unobstructed (Schäfer grade 0 or 1), after CLP 91% of the patients were unobstructed and after electrovaporization 72% were unobstructed while the remaining 28% became equivocal (Schäfer grade 2). Effective capacity was defined as the maximum cystometric capacity minus the residual volume after voiding. The average increase in all groups was at least 50%. This increase was the result of an increase in maximum cystometric capacity and a concomitant decrease in postvoid residual volume. The prevalence of detrusor instabilities halved in all groups. A clinical relevant postvoid residual urine volume was defined as a volume of more than 10% of the maximum cystometric capacity. In all groups there was a decrease of at least 60%. Maximum urinary flow rate (Qmax) was measured at several intervals, but only at baseline and after 6 months we were able to analyze enough patients to evaluate these changes statistically. There were no significant changes in the increases in Qmax between the different groups. Qmax increased in all groups from about 10 ml/s to about 24 ml/s after 6 months. There were almost no technical problems with the new techniques that made it necessary to cross-over to TURP. Results in the CLP group and electrovaporization group are comparable to other studies that have been performed with these modalities.

TURP has been the gold standard for many decades, but is associated with a relatively high morbidity. This challenged many to develop techniques with a lower mortality and morbidity, but with still a good improvement in symptomatic and subjective parameters. Chapter 5 compares symptomatic and subjective changes using AUA questionnaires and compares perioperative parameters, morbidity and mortality of the three different surgical modalities.
Mean operation time was within one hour in all groups and did not differ significantly in all groups. Haemoglobin did not change significantly within the CLP and electrovaporization groups, though there was a significant change ($p<0.001$) within the TURP patients. Drainage time and hospitalization were very similar and no significant differences were demonstrated. Intraoperative complications showed some differences between the groups. Capsule perforation was highest in the TURP group (10%), bleeding requiring electrocoagulation or conversion was most often necessary in CLP (4% and 8% respectively) and technical failures never happened in the TURP group, but 3 and 2 times in the CLP and electrovaporization groups respectively. Urinary retention was highest in the CLP group. Two men died in the TURP group after 4.5 and 6 months and no men died within 12 months in the other groups. There were no significant differences in the changes of the AUA validated questionnaires over 12 months Postoperatively. The average decreases in these scores were for I-PSS from about 18 to about 6, for SPI from about 12 to about 3, for BII from about 10 to about 3 and for the QoL score from about 3.8 to 1.1. Frequency during daytime and during nighttime decreased significantly in all groups, but again no statistically significant differences could be detected. Some specific morbidity and symptomatic parameters were measured using self-developed questionnaires. These demonstrated a higher urinary incontinence in the TURP group. Paradoxically, a higher postoperative haematuria was shown in the CLP group.

Chapters 4 and 5 demonstrate only small differences between the three treatment modalities in urodynamic findings after 6 months and in symptomatic and subjective changes up to twelve months. As mentioned before, it is important to compare results on a long-term basis. Such study was performed and is described in chapter 6. All patients that were included during the course of the study, were reinvited to the outpatient department in fall 2002. Only patients who were operated on for more than 18 months ago were included. In this way, follow-up times varied individually from 1.5 to 7 years. The same questionnaires and tests were used as during the 12 months follow-up: I-PSS, SPI, QoL question, BII and the selfdeveloped questionnaires about specific morbidity and symptoms including number of voids during daytime and nighttime. If patients were able to visit the outpatient department, they were asked to perform uroflowmetry. After 1 year, there were still 41 TURP patients, 37 laser patients and 34 electrovaporization patients available for further follow-up, making a total of 112 patients. In fall 2002, ninety-eight patients or relatives responded finally (response rate 88%). Fourteen patients did not respond (12%). Eighty-one responding patients returned all questionnaires and these could be used for long-term analysis (83% of the responders). Another 6 had been re-operated (6%), 2 were excluded because of morbidity (2%), 2 were not willing to cooperate (2%) and 7 patients died (7%) according to relatives. Fifty-nine responding patients performed free uroflowmetry (60% of the responders).

The response rate of 88% enabled an adequate follow-up. However, patients were only analyzed once after their one year follow-up, resulting in a large variation in individual follow-up time. Secondly, the low number of patients creates a low power, so that significant differences might not always be detected. In each treatment group there were 24 to 30 patients scattered over the long time interval, with 2 to 6 patients per follow-up year. Therefore, patients were divided over two follow-up time intervals of 3 years each: a follow-up time of 1-4 years and a follow-up time of 4-7 years. In this way, data can be presented and interpreted more comprehensively. Statistical analyses were only performed on data from patients who were seen at baseline and at long-term follow-up.

The results of this follow-up demonstrate a high durability for symptomatic and subjective relief. The various AUA validated questionnaires show only a small rise with no statistical significant differences between the treatment modalities. This rise might partially be explained by normal aging in which symptoms and bothering increase. Frequencies during daytime and nighttime were for all groups during long-term follow-up very similar compared to the values 1 year postoperatively. We have no good explanation for the significant higher mean nocturia (1.9) in laser patients after 4-7 years. Maximum uroflow showed lower values after long-term follow-up: about 20 ml/s after 1-4 years between 16 and 19 ml/s after 4-7 years follow-up. These decreases can not be fully explained by normal aging as was observed in other studies. The specific morbidity and symptom questionnaires demonstrated few differences between the treatment groups and most parameters were scored only incidentally.

The committee on the economics of BPH from the International Consultation on BPH from 2000 recommended that future studies on treatment strategies should incorporate an economic analysis. Until today, relatively few studies have analyzed economic parameters in BPH treatment studies. Chapter 7 compares the costs of the three surgical treatments in our randomized trial. Previous chapters concluded only minor differences in these outcome results, even after long-term follow-up. Obvious differences were seen in the equipment costs, with laser being the most expensive. Electrovaporization has the lowest costs and laser costs are slightly higher than TURP costs (about 10% higher). Hospital stay decreased over the course of the trial most in laser and electrovaporization patients. A sensitivity analysis was performed and recalculated costs became almost equal for laser compared to TURP. Total costs for electrovaporization were still lower than the other modalities.

In chapter 5, it was shown that their were no statistically significant changes in haemoglobin levels in the CLP group. This is caused by the combination of direct tissue ablation by vaporization and coagulation of the remaining tissue. TURP leaves an almost native layer of tissue behind that causes more blood loss. This makes TURP contra-indicated for men using anticoagulants or with bleeding disorders. Only small studies have been performed thus far with the use of laser in this high-risk group. Chapter 8 compares the results of a group of high-risk (HR) men treated with CLP or the combination of CLP with VLAP (hybrid therapy). High-risk patients were defined as men using anticoagulants (acenocoumarol or fenprocoumon), platelet aggregation inhibitors or with various bleeding disorders. Hybrid therapy was used in the first years and replaced by CLP, because the latter was easier to use and demonstrated equal results. A group of normal risk patients from our randomized, controlled trial was used as a control group. In the HR groups there were obvious symptomatic and subjective improvements 6 months postoperatively measured by the AUA validated questionnaires: I-PSS, SPI, QoL question and BII. However, these changes were not always statistically significant. Urodynamics after 6 months showed a good desobstruction in all groups. However, there was only a minor increase in maximum flow in the HR-CLP group. Partially, this can be explained by a decrease in contractility within this group. Haemoglobin decrease was not significant in the control group and small (0.4 mmol/l) but significant within the HR groups. However, the clinical relevance of these changes is small, demonstrating intraoperative safety. Drainage times were almost equal between the two CLP groups and were significantly shorter than in the HR-hybrid group. This difference can be explained by direct obtained desobstruction in CLP caused by vaporization. VLAP causes more tissue necrosis and requires longer catheterization. However, hospital stay did not differ significantly between the HR groups. HR-CLP patients were kept some extra days in hospital to watch them carefully. Retrospectively, this regimen might have been too careful, because only 3 out of the 19 patients had a clot retention and this were always men with gross haematuria after catheter removal. Possibly, there are slightly more intraoperative bleedings and postoperative clot retentions in the HR-CLP group. Although some other studies reported blood transfusions, these were never necessary in the present study.

CONCLUSIONS

Improvements after transurethral prostate resection are significantly associated with decreased bladder outlet obstruction. However, also increase in effective capacity, absence of prevalence of instabilities and residual volumes contribute to a significant decrease in symptoms and bother. Therefore also men who were preoperatively unobstructed or equivocal may benefit significantly from TURP. The presence or absence of urethral obstruction in men with LUTS associated with prostatic enlargement (BPE) should be a less decisive factor in treatment choice. The absence of obstruction should never be an exclusion criterion for TURP.

Our randomized, controlled trial comparing TURP, contact laser prostatectomy and electrovaporization demonstrates in general only small differences between these different modalities. Urodynamically there are no statistically significant differences 6 months Postoperatively. Uroflowmetric results are very similar and increase with a factor of 2.4 after 6 months. AUA validated questionnaires demonstrate no statistically significant differences over the course of 12 months between the three groups. Improvement of I-PSS, SPI, QoL question and BII are very similar. Intraoperative and postoperative morbidity show some differences between the three modalities: capsule perforations are more seen in TURP, bleeding intraoperatively more in CLP, although significant changes in haemoglobin are only seen in TURP. Long-term follow-up demonstrates durable results for symptomatic and subjective parameters using the same questionnaires as used before. Maximum uroflowmetry results decreases to about 150% of the baseline values. A cost analysis of these modalities showed that electrovaporization had the lowest costs, followed by TURP and CLP, which costs are almost similar.

CLP and the combination of CLP with VLAP demonstrate to be safe methods in treating high-risk patients using anticoagulants or with bleeding disorders. There are statistically significant and clinical relevant improvements in most subjective and urodynamic parameters, also when compared to a group of normal-risk men who were treated with CLP.

FUTURE PERSPECTIVES

At this moment, TURP is still the most practiced surgical modality for men with BPH and moderate to severe LUTS worldwide. And it will stay the gold standard for BPH surgery probably for many more years for reasons that were mentioned before. Many, mostly academic, centers are nowadays involved in developing and testing new minimally invasive methods to treat these patients. Today's residents in urology will become more familiar with surgery that is different from TURP. This will make them more accessible to new techniques, contrary to many urologists who have learnt only TURP and performed this throughout their professional career.

At our center contact laser prostatectomy is used on a regular base for patients using anticoagulants or with bleeding disorders. More and more selected normal risk patients are also treated with contact laser on a short stay base with only one overnight stay or even in a daycare setting. These practices will probably become more practiced in the future and the logistical and financial hospital structures should adapt to this new situation. Other centers use different minimally invasive options like TUMT, which is often performed in an outpatient based structure. Slowly, several of these new modalities will probably be adapted by several non-university hospitals.

In the near future, the patient with LUTS associated with BPH might be able to choose from many treatment options, varying from pharmacotherapy to several minimally invasive (surgical) modalities including TURP. New developments but also the arduous evaluation processes of recently introduced methods should continuously be stimulated. This in order to offer the constantly increasing number of men with LUTS always the optimal treatment.

CHAPTER 10

Nederlandse samenvatting

Deze samenvatting beoogt het geven van een beknopt overzicht van de inhoud van dit proefschrift in een voor niet-medici begrijpelijk Nederlands. Het blijkt echter toch altijd weer moeilijk voor hen de inhoud begrijpelijk en duidelijk samen te vatten. Laat het in ieder geval beschouwd worden als een oprechte poging daartoe. Ik vind het de moeite waard om uit te leggen wat urologie is en de resultaten van dit proefschrift toegankelijk te maken.

De urologie is een specialisme binnen de geneeskunde dat zich bezig houdt met ziekten aan de organen van de urinewegen. Van ‘boven-naar-beneden’ zijn dit de nieren, de urineleiders, de blaas en de plasbuis. Bij mannen komen daar nog de prostaat en de uitwendige geslachtsorganen bij. Deze organen vormen een vrij duidelijk afgebakend deel van het lichaam waar het nodige mee mis kan gaan. Er kunnen ontstekingen optreden, steenvorming kan plaatsvinden, er bestaan allerlei aangeboren afwijkingen en er kunnen tumoren ontstaan.
Met name in de prostaat ontstaan vaak tumoren. Dit kastanje vormige orgaan, ook wel de *voorstanderklier* genoemd bevindt zich direct onder de blaas. De exacte functie van dit orgaantje is niet geheel duidelijk. Het produceert prostaatvocht, wat belangrijk is bij onderdelen van het transport van zaadcellen. Er is meer bekend over wat er allemaal mis kan gaan met de prostaat, dan wat nu precies verder de functie van dit orgaan is.
Met het stijgen van de leeftijd verandert er bij de meeste mannen nogal wat in de prostaat. Cellen gaan zich delen en dit leidt tot een goedaardige of een kwaadaardige tumor. Het woord tumor betekent feitelijk alleen dat er iets in omvang toeneemt en dit hoeft niet noodzakelijk kwaadaardig te zijn. Een kwaadaardige tumor betekent dat er sprake van kanker is. In dit proefschrift gaat het niet om prostaatkanker, maar juist om goedaardige prostaatvergrotingen. Dit laatste wordt ook wel BPH genoemd (<u>B</u>enigne <u>P</u>rostaat <u>H</u>yperplasie), zoals in de titel van dit proefschrift is te lezen. Bij een aanzienlijk deel van de mannen boven de 30 jaar gaat de prostaat groeien; bij de een langzaam, bij de ander snel. Dat kan betekenen dat de plasbuis, die midden door deze klier loopt, dichtgedrukt wordt.
Als dat gebeurt, wordt het voor de blaas moeilijker om tijdens het plassen alle urine via de plasbuis naar buiten te krijgen. Als reactie gaat de spierwand van de blaas verdikken, maar toch wordt de plasstraal vaak minder krachtig. Daarnaast zijn er nog vele andere verschijnselen of symptomen die kunnen optreden, zoals het vaker moeten plassen (zowel overdag als ’s nachts), sterke aandrang om te moeten plassen of het zogenaamde ‘nadruppelen’. Vervelende klachten die vaak, maar niet altijd, samengaan met een goedaardige vergroting van de prostaat. Vele andere afwijkingen aan de urinewegen kunnen soortgelijke klachten geven. Deze klachten kunnen ook optreden bij mannen met prostaatkanker, maar het is niet zo, dat mannen met plasklachten hier meer kans op hebben dan mannen zonder

plasklachten. Prostaatkanker en goedaardige vergroting van de prostaat (BPH) zijn twee aparte ziekten, hoewel ze wel samen bij één man kunnen voorkomen.
Mannen die hinder hebben van hun plasklachten of zich hier zorgen over maken, komen bij de huisarts of de uroloog terecht. Het vragen naar de precieze klachten en het verrichten van aanvullend onderzoek is nodig om de juiste diagnose te stellen. Dit aanvullende onderzoek bestaat uit het verrichten van een rectaal onderzoek (toucher) waarbij de prostaat gevoeld kan worden. Verder wordt er meestal bloedonderzoek gedaan, wordt de straalkracht tijdens het plassen gemeten, wordt een echo gemaakt van de prostaat en worden er enkele vragenlijsten gebruikt om een goed inzicht te krijgen in de hoeveelheid symptomen en de mate waarin deze symptomen klachten geven. In sommige gevallen wordt tevens een urodynamisch onderzoek verricht. Hierbij worden, met gebruik van speciale drukmetertjes die in de blaas worden gebracht, de blaas en plasbuis helemaal doorgemeten. Zo kan bijvoorbeeld worden gemeten in welke mate de prostaat het plassen belemmert.
Als duidelijk is dat de plasklachten worden veroorzaakt door BPH, bestaan er diverse behandelmogelijkheden. De keuze hangt af van de mate waarin er klachten bestaan en uit de voorkeur van patiënt en arts voor bepaalde middelen. Soms is het genoeg om uit leggen waar de klachten vandaan komen en de patiënt gerust te stellen dat er geen kanker is. Er zijn tegenwoordige diverse medicijnen die de klachten kunnen verminderen en er kan geopereerd worden. In dit proefschrift gaat het om verschillende operaties die mogelijk zijn.
Tot ongeveer 1960 werd er geopereerd via een snede in de onderbuik. Daarna werd een nieuwe techniek steeds populairder. Het was technisch mogelijk geworden om met behulp van speciale lichtbronnen en verfijnde optische lenzen toegang te krijgen tot de prostaat via de plasbuis. Dit wordt transurethrale (=door de plasbuis) scopie (=kijken) genoemd. Door deze natuurlijke toegangsroute te gebruiken is het niet meer nodig om een snede te maken en dus een litteken achter te laten. Een elektrisch lisje aan het einde van een smalle buis (=scoop) maakt het mogelijk om stukjes prostaatweefsel weg te snijden. Deze techniek wordt TURP genoemd (=Trans Urethrale Resectie van de Prostaat) en is de gouden standaard voor chirurgie bij BPH.
Met deze techniek zijn goede resultaten te behalen, maar er komen vaak bijwerkingen voor zoals bloedverlies. Dit leidt tot ziekte en zelfs sterfte tijdens en na de operatie. Sinds het begin van de jaren negentig, nu ruim tien jaar geleden, zijn er vele nieuwe technieken uitgeprobeerd. Het doel is om dezelfde goede resultaten van TURP te behalen, maar dan met minder bijwerkingen. In dit proefschrift wordt de gouden standaard TURP vergeleken met twee van deze nieuwe technieken: een laser en een elektrisch cilindertje. Bij de laser wordt er laserlicht via glasvezels door de scoop geleid die in de plasbuis wordt gebracht. Aan het einde zit een saffieren bolletje met een zwart oppervlak dat door het laserlicht extreem heet wordt. In contact met de prostaat verdampt het prostaatweefsel en blijft er een dichtgeschroeid

laagje achter. Dit type laser wordt de contact laser genoemd. De techniek met het elektrisch cilindertje wordt electrovaporizatie genoemd en lijkt veel op de contact laser. Elektriciteit verhit een cilindertje aan het uiteinde van de scoop. Dit cilindertje, met kleine tandjes, wordt dan tegen de prostaatkwabben aan gerold, waardoor het weefsel eveneens verdampt en dichtschroeit.

Het eerste hoofdstuk, de inleiding, behandelt voor een groot deel wat hierboven uitgebreid aan de orde is gekomen.

In het tweede hoofdstuk wordt gekeken naar het urodynamisch onderzoek. Bij dit onderzoek worden blaas, prostaat en plasbuis ‘doorgemeten’ om inzicht te krijgen in het functioneren hiervan. Dit inderzoek werd uitgevoerd bij patiënten die een TURP ondergingen. Zowel voor de ingreep als zes maanden later werd dit gedaan in combinatie met het invullen van diverse vragenlijsten over plasklachten. De resultaten van de vragenlijsten werden vergeleken met de resultaten van het urodynamisch onderzoek. Op deze wijze werd inzicht verkregen in de onderlinge relatie. Dit inzicht maakt het mogelijk om op basis van het urodynamisch onderzoek tot op zekere hoogte te kunnen voorspellen wat de gevolgen van een prostaatoperatie zullen zijn.

In het derde hoofdstuk wordt dieper ingegaan op een bijzondere groep mannen met plasklachten. Zij hadden weliswaar een vergrote prostaat, maar deze drukte de plasbuis vrijwel niet of heel weinig in. Deze mannen werden geopereerd middels een TURP en vergeleken met mannen die een vergrote prostaat hadden met wel een duidelijk vernauwde plasbuis. De mannen uit de laatste groep bleken, zoals te verwachten, de meeste baat te hebben bij de ingreep. Opvallend was echter, dat de meeste mannen uit de groep met een ‘openstaande’, vergrote prostaat eveneens vrij goede verbeteringen lieten zien. Vaak waren de verschillen tussen deze twee groepen slechts gering. Dit maakt duidelijk dat de oorzaak van plasklachten niet simpelweg ligt in een prostaat die de plasbuis dichtdrukt en dat de behandeling van TURP mogelijk niet alleen berust op het verbeteren van de doorgankelijkheid van de prostaat

In het vierde tot en met het zevende hoofdstuk wordt de TURP op verschillende manieren vergeleken met de contact laser en de electrovaporizatie. Dit is een studie die op de afdeling urologie van Universitair Medisch Centrum Utrecht (UMC Utrecht) is uitgevoerd tussen 1996 en 2002. Hieraan deden patiënten mee met plasklachten samengaand met goedaardige prostaatvergroting. Indien zij toestemden om in studieverband geopereerd te worden, bepaalde het lot welke van de drie technieken tijdens de operatie gebruikt zou worden.

In het vierde hoofdstuk wordt aangetoond dat er tijdens het urodynamisch onderzoek geen verschillen zijn gevonden tussen de drie chirurgische methoden. Zowel voor de operatie als 6 maanden na de operatie werd dit onderzoek verricht, waarbij met fijne meetinstrumenten de blaas, prostaat en plasbuis werden ‘doorgemeten’. Er bleken goede verbeteringen te zijn in de straalkracht en de weerstand over de prostaat was fors verminderd.

In het vijfde hoofdstuk wordt gekeken naar de bijwerkingen tijdens en na de operatie. Er bleek over het algemeen duidelijk minder bloedverlies op te treden bij de twee nieuwe technieken in vergelijking met TURP. Toch trad er af en toe een bloeding op die het nodig maakte om terug te vallen op de bekende oude manier, de TURP. In het jaar dat op de operatie volgde, bleken er geen duidelijke verschillen waarneembaar te zijn tussen de drie groepen.

In het zesde hoofdstuk wordt gekeken naar enkele lange termijn resultaten. Een techniek kan op korte termijn fraaie resultaten tonen, maar het is belangrijk om te laten zien of deze resultaten ook duurzaam zijn. Alle patiënten die meer dan anderhalf jaar tevoren geopereerd waren, werden gevraagd vragenlijsten in te vullen en zo mogelijk naar de polikliniek te komen. In totaal verkregen we van 88% van de patiënten resultaten. Patiënten waren anderhalf tot zeven jaar geleden geopereerd. De gemiddelde tijd tussen operatie en dit vervolgonderzoek was 4,3 jaren. Zoals te verwachten waren de symptomen en klachten weer enigszins toegenomen en was de straalkracht afgenomen. Er waren echter slechts geringe verschillen tussen de drie groepen en de resultaten waren nog altijd beduidend beter dan voor de operatie. Hiermee werd de duurzaamheid van de verschillende technieken aangetoond. Een beperking is, dat we alle patiënten slechts eenmaal op de lange termijn gezien hebben en dat voor iedere patiënt de tijd tussen de operatie en het lange termijn vervolgonderzoek verschillend was.

In het zevende hoofdstuk wordt gekeken naar kosten die samengaan met de verschillende operaties. De kosten voor de gezondheidszorg stijgen enorm en dit maakt het noodzakelijk om kosten van een behandeling af te wegen tegen de resultaten die er mee te boeken zijn. Om de kosten van een ingreep te berekenen werd gekeken naar een aantal kostenaspecten: kosten van apparatuur tijdens de operatie, het aantal dagen dat patiënten in het ziekenhuis moesten blijven en kosten van extra behandelingen die nodig waren als de ingreep niet goed was gegaan. Deze kosten werden vergeleken met de resultaten van de vragenlijsten en straalkrachtmetingen na 1 jaar. De kosten voor laser waren het hoogst, maar deze patiënten konden, net zoals de electrovaporizatie patiënten, sneller uit het ziekenhuis ontslagen worden dan de TURP patiënten. Aangezien de resultaten na 1 jaar vergelijkbaar waren, leidde dit tot de beste kosten-baten verhouding voor de electrovaporizatie, gevolgd door de TURP en laser. De laatste twee verschilden weinig.

In het achtste hoofdstuk, tevens het laatste wetenschappelijke artikel, wordt een speciale risicogroep van mannen met plasklachten en BPH geopereerd met lasers. Deze mannen gebruiken bloedverdunners of hebben bloedingsziekten, zodat ze geen gewone TURP mogen hebben. Er werd geopereerd met de contact laser of een combinatie hiervan met een zijwaards schijnende laser. De resultaten werden vergeleken met de mannen uit de voorgaande hoofdstukken die geen verhoogd bloedingsrisico hebben. Deze studie laat zien, dat er veilig geopereerd kan worden met deze lasers. De resultaten zijn weliswaar iets minder goed dan bij de normale patiënten, maar er worden duidelijke verbeteringen geboekt.

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CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren op 19 november 1972 in Nijmegen. In 1991 slaagde hij voor het eindexamen Atheneum B op de scholengemeenschap St. Ursula in Horn (Limburg). In 1992 eindigde hij zijn studie scheikundige technologie aan de TU in Eindhoven om met geneeskunde aan te vangen aan de universiteit van Diepenbeek in Belgie. In 1993 kon hij deze studie vervolgen aan de universiteit van Utrecht. In 1997 werkte hij enkele maanden op het Barcroft laboratorium in de White Mountains in Californie (VS). Onder supervisie van prof. dr. J.B. West deed hij onderzoek op het gebied van de hoogtefysiologie. Zijn medische graad verkreeg hij in april 2000. Hierop aansluitend begon hij met onderzoek bij de vakgroep urologie van het Universitair Medisch Centrum Utrecht (UMCU) onder leiding van prof. dr. T.A. Boon. In januari 2001 werd aangevangen met de werkzaamheden die tot deze promotie hebben geleid. Tegelijkertijd werd gestart met het verrichten van klinische werkzaamheden op dezelfde afdeling. In februari 2003 werd in het kader van de opleiding urologie begonnen met de vooropleiding chirurgie in het Rijnstate ziekenhuis te Arnhem onder leiding van dr. J.H.G. Klinkenbijl. Zijn verdere opleiding tot uroloog zal volbracht worden in Tilburg en Utrecht.