

Transurethral resection of the prostate

Studies on efficacy, morbidity and costs

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UNIVERSITY OF GOTHENBURG

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I dedicate this work to my family...

Mikaela, Ellen, Isak and Miriam

Den mätta dagen, den är aldrig störst.

Den bästa dagen är en dag av törst.

Nog finns det mål och mening i vår färd,

Men det är vägen som är mödan värd.

Det bästa målet är en nattlång rast,

Där elden tänds och brödet bryts i hast.

På ställen, där man sover blott en gång,

Blir sömnen trygg och drömmen full av sång.

Bryt upp, bryt upp! Den nya dagen gryr,

Oändligt är vårt stora äventyr.

Karin Boye: I rörelse

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ABSTRACT

Lower urinary tract symptoms (LUTS), based on benign prostatic enlargement (BPE), are increasingly common, in ageing men. A considerable amount of men will ultimately progress with deteriorating symptoms or with the occurrence of complications secondary to obstruction of the bladder outlet, for example, urinary retention (UR). These subjects need surgery. Transurethral resection of the prostate (TURP) is the gold standard surgical intervention for symptoms associated with BPE. Over time, the TURP procedure has evolved due to manifold technical improvements and these progresses, coupled with improved surgical skill, are thought to have led to additional improvements regarding voiding outcomes, coupled with a decreased morbidity and mortality. The aims of this thesis were to explore and elucidate the effects of TURP, in a non-academic setting, including functional outcomes, complications and healthcare costs. All consecutive men subjected to a TURP procedure due to BPE at Skaraborgs Hospital during the periods 2010-2012 and 2017-2019 were identified and data retrieved from the hospital records. All men were followed-up for 3 months postoperatively and more if deemed necessary. Responders were defined according to criteria set up by de Wildt. Complications were graded in accordance with the Clavien-Dindo system. In **Paper I**, men with bothersome LUTS and men in UR reported response rates of 95% and 83% respectively indicating that TURP is a successful procedure in both these patient categories. In **Paper II**, the incidence of major complications was low, during hospital stay (2.3%) and between hospital discharge and follow-up (3.4%). Late complications, requiring endourological re-intervention occurred in 9.7%. In **Paper III**, we followed the fate of the 35 non-responders and found that 11 men were finally judged to have satisfactory voiding parameters, 16 men utilized clean intermittent self-catheterisation to varying degrees, 7 men had to use an indwelling catheter indefinitely, and only one man still suffered from bothersome LUTS. In **Paper IV**, we analysed all in-hospital expenses of 122 men subjected to TURP and found that the median cost for this procedure was 37343 SEK (IQR 29852-44260). The main drivers of total cost were length of hospital stay, the surgical procedure and anaesthesia related costs. The main factor that increased total cost per patient was the occurrence of complications. **In summary**, transurethral resection of the prostate is a rewarding operation in men with UR or with bothersome LUTS. Men with preoperative UR constituted most of non-responders. There was a low use of invasive urodynamic investigations after surgery. In the end, nearly one in three non-responders had a fair outcome with or without redo-surgery. TURP in routine clinical care was linked with a low incidence of serious complications. TUR syndrome was very rare. A small amount of patients needed the endourological treatment to be repeated. The main factor affecting total cost for a TURP procedure was the occurrence of postoperative complications.

Keywords: benign prostatic hyperplasia, urinary retention, transurethral resection of the prostate, complications, healthcare costs

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SAMMANFATTNING PÅ SVENSKA

Godartad prostataförstoring med avflödeshinder är en vanlig sjukdom som drabbar den åldrande mannen. Prostataförstoring kan leda till betydande besvär med vattenkastningen och en negativ inverkan på livskvalitén. Det har tidigare visats att en tredjedel av den manliga befolkningen över 50 år i Sverige lider av vattenkastningsbesvär till varierande grad. Som regel erbjuds dessa män behandling med läkemedel, med målet att minska besvären och ibland även minska storleken på prostatakörteln. Emellertid kommer en betydande andel män så småningom att försämrats i sina symtom eller utveckla någon form av komplikation till blåstömningsproblem som kan bli följden av ett avflödeshinder, till exempel urinstopp. Dessa män behöver åtgärdas kirurgiskt.

Transuretral resektion av prostata (TURP) betraktas som standardbehandling vid operation mot godartad prostataförstoring med avflödeshinder. Ungefär 4000 TURP-operationer utförs per år i Sverige. Ingreppet utförs via ett instrument som förs in i urinröret, under ryggbedövning eller narkos, och en metallslynga som skär ut bitar av prostatan vilka sedan spolats ut genom instrumentet. Utifrån kliniska studier, för det mesta baserat på data från stora centra, har TURP visat sig leda till utmärkta resultat avseende förbättrad vattenkastning. Nio av tio män har angett en normal vattenkastning efter tio års uppföljning både med objektiva och subjektiva mått mätt. Risken för olika sorters komplikationer, har dock varit ett bekymmer och som lett fram till en utveckling i så kallade skonsammare metoder.

De senaste decennierna har frambringat flertalet betydande tekniska utvecklingar avseende instrumentariet och tilltagande kirurgisk erfarenhet avseende metoden. Dessa anses ha bidragit till ytterligare förbättring avseende metodens effektivitet och till minskad komplikationsfrekvens. År 2011 genomfördes en systematisk litteraturoversikt på godartad prostataförstoring med avflödeshinder av Statens beredning för medicinsk utvärdering (SBU), en statlig myndighet som utvärderar hälso- och sjukvårdens metoder. SBU konstaterade att det fanns en del kunskapsluckor avseende TURP-metodens effekt i den kliniska vardagen.

Syftet med denna avhandling är att undersöka och belysa effekterna av TURP, i en icke-akademisk miljö, på män med besvärande vattenkastning eller som drabbats av urinretention på grund av prostataförstoring. Vi använde oss av en prospektivt insamlad kohort av 354 män under åren 2010-2012 samt en retrospektivt insamlad kohort av 122 män från åren 2017-2019

som genomgått TURP på Skaraborgs Sjukhus i Skövde på grund av godartad prostataförstoring.

Resultaten visade att nästan hälften av männen genomgick en TURP operation på grund av urinretention. Nästan en av fem män hade betydande bakomliggande sjuklighet och nio av tio operationer utfördes i ryggbedövning. I **artikel I** kunde vi visa att 95% av de män som opererats på grund av besvärande vattenkastning och 83% av de med urinretention fick ett lyckat resultat efter ingreppet. TURP leder till betydande förbättring avseende symtom, besvärsgrad, urinflödesmätning och blåstömningsförmåga. I **artikel III** kunde de män som betraktades få icke gynnsamma resultat efter ingreppet sedan följas över en treårsperiod för att kartlägga deras slutgiltiga öde avseende vattenkastningen. Merparten av de icke gynnsamma fallen hade opererats på grund av urinretention. En analys av den postoperativa utredningen av dessa män kunde bland annat visa på en bristfällig standardiserad uppföljning på kliniken där framförallt nyttjandet av avancerad urodynamisk undersökning var anmärkningsvärt låg. I **artikel II** kunde vi visa att allvarliga komplikationer var ovanliga både under vårdtiden och fram till planerat återbesök tre månader senare. En av tio män behövde genomgå ytterligare ett ingrepp inom en femårsperiod. Slutligen, i **artikel IV** kunde vi se att det som framförallt påverkar kostnaden under ett vårdtillfälle för en TURP operation är vårdtiden, själva ingreppet, anestesi samt förekomsten av komplikationer.

De viktigaste slutsatserna blir att TURP idag fortfarande är en bra metod för att undanröja ett avflödeshinder orsakad av prostataförstoring oavsett om en man lider av besvärande vattenkastning eller har drabbats av urinretention. Dessa två kategorier av män skiljer sig åt i bakomliggande parametrar och borde således analyseras separat när TURP jämförs mot konkurrerande metoder. Det har visat sig att en stor andel av icke gynnsamma fall till slut kommer att vara nöjda med sin vattenkastning, med eller utan ett förnyat ingrepp. Vidare är TURP behäftad med en väldigt låg risk för allvarliga komplikationer. Slutligen så är kostnaderna för ett TURP-vårdtillfälle framförallt påverkade av förekomsten av komplikationer vilket understryker betydelsen av att undvika och förhindra att de uppstår.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. **Sagen E**, Hedelin H, Nelzén O, Peeker R. Defining and discriminating responders from non-responders following transurethral resection of the prostate. *Scand J Urol* 2018;52(5-6):437-444.

- II. **Sagen E**, Namnuan RO, Hedelin H, Nelzén O, Peeker R. The morbidity associated with a TURP procedure in routine clinical practice as graded by the Clavien-Dindo system. *Scand J Urol* 2019;53(4):240-245.

- III. **Sagen E**, Nelzén O, Peeker R. Transurethral resection of the prostate: Fate of the non-responders. *Scand J Urol* 2020 Sep 4:1-6. Online ahead of print.

- IV. **Sagen E**, Javid R, Bencherki A, Liivrand L, Nelzén O, Peeker R, Månsson M. Patient related factors affecting in-hospital costs of TURP. *Submitted 200830*.

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ABBREVIATIONS

ASA	American Society of Anaesthesiologists
AUA	American Urological Association
AUR	Acute urinary retention
BMI	Body Mass Index
BOO	Bladder outlet obstruction
BPE	Benign prostatic enlargement
BPH	Benign prostatic hyperplasia
DRE	Digital rectal examination
DUA	Detrusor underactivity
ED	Erectile dysfunction
EAU	European Association of Urology
IPSS	International prostate symptom score
LUTS	Lower urinary tract symptoms
MIST	Minimally invasive surgical therapy
OAB	Overactive bladder
PSA	Prostate specific antigen
PVR	Postvoid residual urine volume
TRUS	Transrectal ultrasound scan
TURP	Transurethral resection of the prostate
TUIP	Transurethral incision of the prostate

DEFINITIONS IN SHORT

Acute urinary retention: a painful, palpable or percussible bladder, when the patient is unable to pass urine.

Chronic urinary retention: a non-painful bladder, which remains palpable or percussible after the patient has voided. Such patients may be incontinent.

Overactive bladder syndrome: distinguished by urinary urgency, with/without urge incontinence, and generally with increased daytime frequency and nocturia.

Detrusor underactivity: a reduced strength or duration of bladder contraction, which results in prolonged emptying of the bladder and/or failure to achieve complete bladder emptying, either at all or within a normal time span.

Detrusor overactivity: a urodynamic observation distinguished by involuntary contractions of the detrusor muscle during the filling phase which may be spontaneous or provoked.

1 INTRODUCTION

Lower urinary tract symptoms (LUTS), caused by an enlarged prostate, are prevalent, in the ageing male [1]. A previous report has shown that one out of three men in Sweden > 50 years of age are troubled by LUTS in various ways [2]. Men with troublesome LUTS are often initially offered pharmacological treatment, with the goal of alleviating symptoms and/or reducing the volume of enlarged tissue. Still, a considerable amount of patients will ultimately progress with deteriorating symptoms or the manifestation of complications secondary to bladder outlet obstruction, for example, urinary retention [3]. These subjects are in need of surgery.

Transurethral resection of the prostate (TURP) is considered the gold standard surgical intervention for symptoms associated with benign prostatic enlargement (BPE) [4, 5] and, in Sweden, approximately 4,000 such operations are currently performed each year [6]. In clinical studies, generally founded on patient cohorts from university hospitals, TURP has been shown to provide outstanding effectiveness, with nine out ten men reporting normal voiding after long-term follow-up [7], objectively and subjectively bettering micturition outcomes and quality-of-life, respectively [8, 9, 10, 11]. However, this operation still conveys a considerable risk of perioperative morbidity with previous studies revealing adverse events including urinary tract infections, the need for blood transfusions due to profound bleeding, electrolyte imbalances and urinary incontinence [12, 13, 14, 15]. Long-term complications include strictures of the urethra, contractures of the bladder neck and re-intervention due to residual prostatic tissue [16, 17, 18].

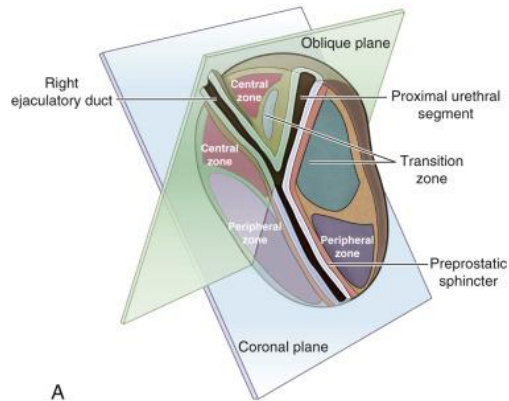
Additionally, some men continue to face considerable dysfunctional and troublesome voiding for a longer time after the operation, without any obvious adverse events from the intervention. Past reports have demonstrated continuing LUTS in up 20% of patients after a TURP operation [19]. Moreover, a substantial amount of subjects still need clean intermittent self-catheterisation (CISC) or a permanent indwelling catheter following TURP [20].

Finally, the economic costs of treating LUTS secondary to BPE are a considerable load and it is certainly reasonable to assume that these costs will continue to rise in the future secondary to the ageing male population and probably also increasing health awareness [21]. The true costs for surgical

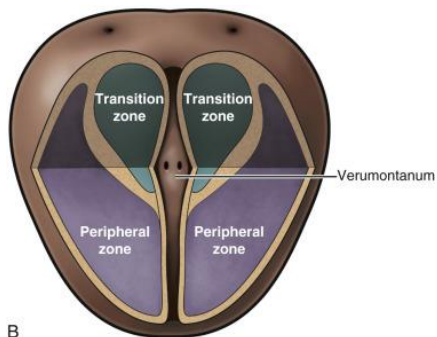
interventions against BPE have been difficult to quantify as treatment costs can differ amid various healthcare systems, regions and institutions.

Over time, the TURP operation has developed thanks to manifold technical advances, including video-assisted monitors, continuous flow devices, loop designs, and adjustments of high-frequency generators [22]. Together with increased surgical skill, these developments are thought to have contributed to additional advances regarding voiding outcomes, coupled with a decreased morbidity and mortality. An extensive systematic literature review on BPE with voiding obstruction was carried out by the Swedish Council on Health Technology Assessment in 2011 [23]. They acknowledged areas that required further investigation; routine clinical practice modern-day data on voiding outcomes following TURP were asked for. The requirement for a universal definition of a 'responder' after TURP was also firmly pointed out. Furthermore, modern data on the morbidity related to a TURP was warranted. The reporting of complications in a validated and standardised manner was also requested [24]. Long-term studies on the fate of men failing to respond to TURP are limited and require further exploring. The review also identified areas in need of further research regarding the healthcare economics of BPE therapy. Specifically, studies on detailed in-hospital expenses were sought for. We set out on a journey with the aim of answering the aforementioned questions.

1.1 THE PROSTATE



A



B

Figure 1. Zonal anatomy of the prostate as first described by McNeal. Sagittal (A) and coronal (B) sections of the prostate showing peripheral zone, transition zone, central zone, the verumontanum, the proximal urethral segment, and pre-prostatic sphincter and the openings of the ejaculatory ducts. (From Roehrborn CG. Benign Prostatic Hyperplasia: Etiology, Pathophysiology, Epidemiology, and Natural History. In Campbell-Walsh-Wein's Urology, 12th edition, Chapter 144, p. 3313) Permission granted.

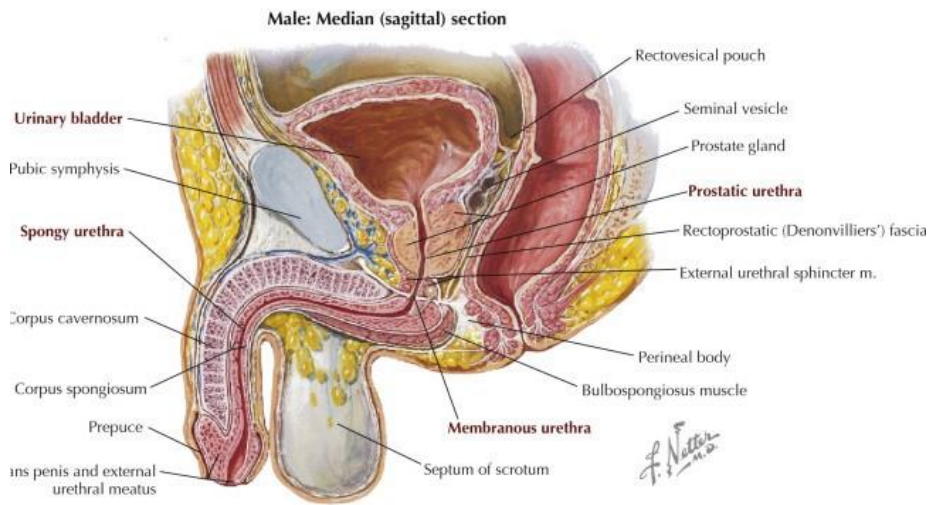


Figure 2. The male pelvis and perineum depicting the prostate gland in relation to adjacent organs. From Netter's Clinical Anatomy (2019), p.233-289. Permission granted.

1.1.1 EMBRYOLOGY

The prostate develops from the distal urogenital sinus, the ventral portion of the cloaca, under the critical influence of testosterone from the foetal gonads. Epithelial outgrowths from the prostatic urethra bud into the surrounding mesenchyme from week 10 of embryologic growth. These buds subsequently signal back to overlying epithelial cells, including prostatic ductal formation. By week 12, there are five groups of tubules that progress to form the lobar anatomy of the prostate. Mesenchymal-epithelial interactions play a pivotal role in development of the prostate, even though the overall developmental process is triggered by androgens via the androgen receptor [25].

1.1.2 ANATOMY

Precise knowledge of the prostatic anatomy is a prerequisite for successful surgical intervention involving the prostate, be it radical prostatectomy, transurethral resection or prostatic biopsy.

The normal prostate is a fibromuscular and glandular organ located within the male pelvis. It resembles an inverted pyramid, is approximately 20-30 mL in volume and is 4 x 4 cm in length and width. Commonly, the prostate is described as having an apex, the lower limit, and a base on which the bladder rests. Throughout its length run and depth run the urethra and the ejaculatory ducts. Related structures include the rectum and the Denonvilliers fascia that lie posterior to the prostate and the paired seminal vesicles and ampullae of the vasa deferentia that lie postero-lateral to the prostate and posterior to the bladder (Figure 2) [26].

The zonal intraprostatic anatomical structure proposed by McNeal [27] (Figure 1), following microscopic examination of the prostate, is now widely accepted. The zones include the peripheral zone, transition zone, central zone, and periurethral zone and the anterior fibromuscular stroma. The individual prostate zones have distinct architectural and molecular features and tend to develop distinct pathologies. For instance, the transitional zone surrounding the urethra has the tendency to develop BPH, making men vulnerable to urinary obstruction, whereas the peripheral zone, which contains most of the glandular elements of the prostate, is the most common site for prostate cancer.

The arterial supply to the prostate most often arises from the inferior vesical artery. This artery then divides into two main branches, the urethral artery and the capsular artery. The urethral arteries enter the prostatovesical junction in the 1- to 5-o'clock and 7- to 11-o'clock positions, with the largest branches situated posteriorly. They then turn caudally, parallel to the urethra, to supply it, the periurethral glands, and the transition zone. As such, in benign prostatic enlargement, these arteries provide the main blood supply of the adenoma. During transurethral resection the most substantial bleeding is commonly encountered at the bladder neck, particularly at the 4- and 8-o'clock positions. Lymphatic drainage is mainly to the obturator nodes and internal iliac nodes [26]. Cavernous nerves from the pelvic plexus contain the parasympathetic and sympathetic fibres to and from the prostate.

Nerves follow branches of the capsular artery branching out further in the glandular and stromal components. Parasympathetic nerves end at the acini and promote secretion; sympathetic fibres cause smooth muscle contraction of the stroma and capsule [26].

1.1.3 PHYSIOLOGY

The development of the prostate gland is governed by the hormone dihydrotestosterone (DHT). DHT is synthesized by the conversion of fetal testosterone, under the influence of the enzyme 5α -reductase. DHT binds to the androgen receptor in the prostate and regulates growth, differentiation, and the functions of the gland. The two main cell types existing in the prostate gland are the epithelial cells and the stromal cells. In the normal prostate, the most common cells are epithelial that are secretory. These cells express prostate specific antigen, acid phosphatase, androgen receptors, and are rich in secretory granules and enzymes. The secretory epithelial cells release their products into acini that drain via ducts into the prostatic urethra [26]. Prostate secretion is composed of biochemically active substances with essential functions for fertility. Both the volume and the constitution of prostate secretion seem to be of great importance for male fertility, increasing sperm motility and aiding passage in the reproductive tracts of both the males and females.

1.2 HISTORICAL BACKGROUND

The word prostate was first used by Herophilus in 300 BC and comes from the ancient Greek word “προστα” which can be translated to “standing in front of...”. The first anatomical description of this gland, in 1538, was presented by Vesalius, while Riolan, in 1649, proposed that prostatic enlargement may subsequently result in urinary retention. Hypertrophy of the prostate and its effects on the bladder, was described by Morgagni in 1761, while carrying out an autopsy on an old man who died of uraemia.

In 1575, Paré performed an operation with the intention to cure a man with prostate adenoma using a punch-type instrument [28]. The balloon dilatation technique for prostatic enlargement was first described by Syng in 1815. In 1850 the French urologist Mercier described a curved metal sound armed with a straight mandarin which was used to apply pressure on the prostate, in particular on its median lobe. Mercier’s compressor was painful and offered little help as it most probably just tore the gland.

In 1830, Ferguson described the option of treating prostatic enlargement by removing the obstructive prostatic tissue. The advent of anaesthetic techniques and the notion of antiseptic surgery progressively led to the development of the suprapubic approach for the removal of stones in the bladder and later for the partial removal of obstructive prostatic tissue. The first transvesical prostatic adenomectomy with enucleation of both lateral lobes and the median lobe was performed by Goodfellow in 1891 but he did not report his feat until 1902 [29]. Instead, Fuller reported the first six cases of suprapubic prostatectomy in 1895. Fuller recognized that the previous unsuccessful results by his colleagues were due to an incomplete removal of the enlarged gland. He was the first to incise the neck of the bladder with scissors to find the space between the adenoma and the capsule, before using his index finger to enucleate both median and lateral lobes. The procedure became popular due to Freyer from London claiming priority over the procedure in 1912. Three decades later, Terence Millin, from Ireland and working in London, developed and popularised the retropubic approach in 1945, where he sutured the capsule and drained the bladder by a urethral catheter [30].

The first endoscope was manufactured by the German doctor Bozzini in 1805. The instrument was termed lightleiter and was a tubular system with a special support for a wax candle, providing light. The lightleiter facilitated

visualisation of the lower urinary tract. Unfortunately, Bozzinis colleagues did not take the endoscope seriously and it was “forgotten” for half a century until 1853, when the French surgeon Desormeaux added an arrangement of mirrors and lenses, consequently refining visualisation. With great credit to T.A. Edison and the discovery of the light bulb, the first polyscope, a prototype of the endoscope, with an electric light source was constructed by the French electrical engineer and inventor Trouve in 1869. The German doctor Nitze designed the forerunner of modern cystoscopes in 1877 [31]. The instrument was constructed by Leiter and was used solely for the examination of the bladder. The device worked by glowing light produced by an electrically heated platinum cable and was fortified with a water-cooling system and telescopic lenses.

Young invented the cold resection technique in 1909, but intraoperative bleeding was difficult to control. Kirwin designed an adapted type of the instrument used for cold resection, in 1931, using coagulation prior to resection, consequently reducing blood loss intraoperatively with better postoperative results [31]. In 1926, loop resection became conceivable when Stern designed the first resectoscope [32]. McCarthy adapted Stern’s resectoscope to cut from the bladder toward the surgeon and combined the working element, which had to be held with both hands, into a casing of Bakelite [33]. The Stern-McCarthy resectoscope became the archetype for all modern resectoscopes still used today. In 1931, Davis developed generators into a box with alternative power, enabling the surgeon to cut or to coagulate intermittently. Davis also presented the foot switch with double action that is still used today, which enables for direct control of both the cutting and the coagulation power. In 1948, Iglesias de la Torre from Havana developed an apparatus that enabled for total control of the electrodes movement forward with one hand, while the backward movement was passively controlled by a spring. Most urologists use the Iglesias model and few use the original Stern-McCarthy resectoscope. Further development in terms of optical systems, for example the Hopkins wide angle lens system, and high-intensity external light sources, coupled with the advent of anaesthetic techniques and antibiotic treatment, contributed considerably to the current role of transurethral resection of the prostate [29].

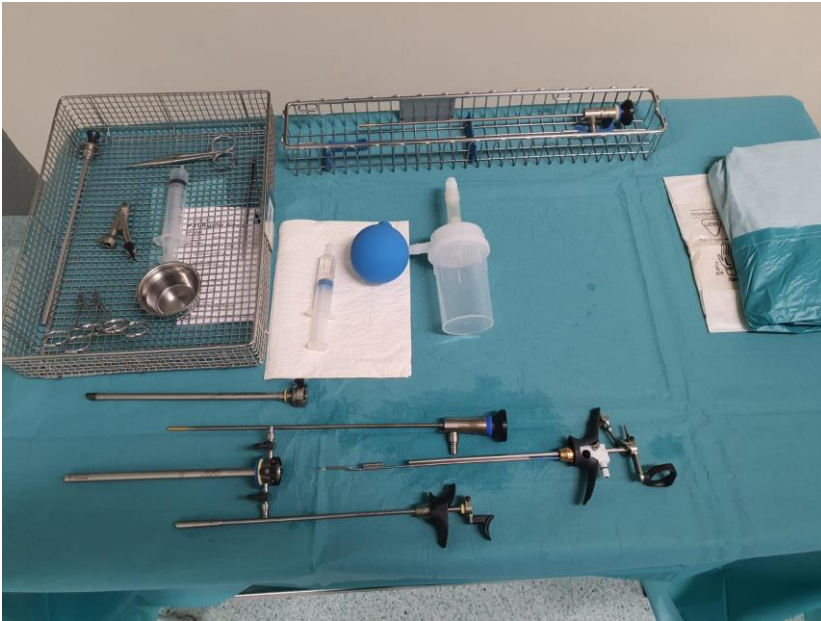


Figure 3. The armamentarium necessary for a TURP procedure. Courtesy of Dr Suleiman Abuhasanein.

1.3 LUTS

Lower urinary tract symptoms are separated into storage, voiding and post-micturition symptoms [34]. LUTS are common, are inconvenient and have a negative impact on quality of life [35, 36, 37]. LUTS are strongly associated with ageing and therefore the related economic burden is expected to rise with future demographic changes [38]. LUTS are also linked with several modifiable risk factors, for example the metabolic syndrome [39], and could lead to an increased risk of cardiac events [40].



Figure 4. The potential causes of LUTS. Source: Oelke M, Bachmann A, Descazeaud A, et al. Guidelines on the management of lower urinary tract symptoms (LUTS), incl. benign prostatic obstruction (BPO): European Association of Urology. 2012; 6-8. Permission granted.

The majority of ageing men experience at least one LUTS although symptoms are commonly slight and not too troublesome [41]. LUTS can progress in different ways; for some men persevering or progressing over longer periods, and for others settling. In the past, LUTS were almost always linked to bladder outlet obstruction (BOO), which is frequently secondary to benign prostatic enlargement (BPE) resulting from the histological condition of benign prostatic hyperplasia (BPH). However, increasing evidence has demonstrated that LUTS are often unconnected to the prostate. A dysfunctional urinary bladder may also cause LUTS in addition to other structural abnormalities of the urinary tract and the adjacent structures [42]. Finally, several non-urological conditions also give rise to urinary symptoms, particularly nocturia.

Trueman et al. studied the influence that BPE-associated LUTS had on the quality of life in a total of 1500 men aged 50 years or older in the UK. Moderate-to-severe LUTS was reported in 41% of men. Respondents experienced a reduction in both quality of life and overall health status as symptoms got worse. Most respondents experienced difficulties with capacity, self-care, activities of daily living, anxiety or depression, and pain or discomfort. Even though LUTS were common in this study, barely 11% were conscious of the pharmacologic or surgical treatments available for BPE. In almost one third of men, watchful waiting was the most frequent primary regimen. This report highlights the requirement for better public education about BPE and its existing therapies [43].

1.4 BPH, BPE, BOO AND BPO

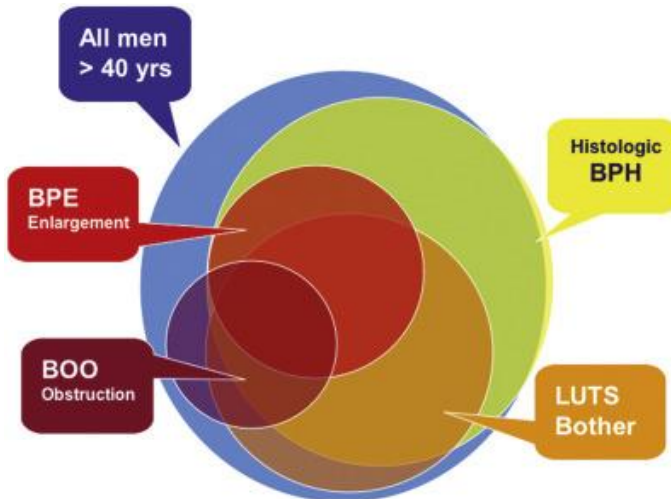


Figure 5. Diagram showing the relationship between histologic hyperplasia of the prostate (BPH), lower urinary tract symptoms (LUTS), benign prostatic enlargement (BPE), and bladder outlet obstruction (BOO). (From Roehrborn CG. Benign Prostatic Hyperplasia: Etiology, Pathophysiology, Epidemiology, and Natural History. In Campbell-Walsh-Wein's Urology, 12th edition, Chapter 144, p. 3313) Permission granted.

Benign prostatic hyperplasia (BPH) denotes a histological diagnosis that refers to the proliferation of smooth muscle and epithelial cells inside the prostatic transition zone. Therefore, BPH is an abbreviation used for the distinctive histological pattern which defines the disease. BPH is a progressive disease typified by prostate enlargement, which might later lead to the onset of lower urinary tract symptoms (LUTS).

Benign prostatic enlargement (BPE) is defined as prostatic enlargement due to histologic BPH. The term prostatic “enlargement” should be used in the absence of prostatic histology. BPE may bring about an increase in urethral resistance, frequently resulting in compensatory alterations of the detrusor muscle. These changes in the physiology of the lower urinary tract might lead to the onset of LUTS.

Bladder outlet obstruction (BOO) is the common term for obstruction during voiding and is characterised by increased detrusor pressure and reduced urinary flow rate. Thus, the term BOO necessitates urodynamic confirmation.

Benign prostatic obstruction (BPO) is a form of bladder outlet obstruction, requiring urodynamic confirmation, and may be diagnosed when the cause of outlet obstruction is known to be BPE, due to histologic BPH.

It should be emphasised that the use of incorrect and varying terminology may lead to misunderstanding among doctors and patients and incorrect treatment of the conditions that underlie male LUTS.

1.5 EPIDEMIOLOGY OF LUTS AND BPH

The development of BPH is a process related to increasing age with a histologic prevalence of approximately 10% for men in their 30s, subsequently increasing to 90% in octogenarians. Androgens and ageing are essential for the development of BPH as shown by the groundbreaking autopsy studies by Berry and colleagues [44] who demonstrated that the incidence of BPH is positively associated with ageing. In particular, it was demonstrated that the normal prostate weighs 20 grams in men aged 21-30 years, however no individual younger than 30 had BPH. Prostate volume also increases with age. In the Olmsted county study, median prostate volumes were 21, 27, 32 and 34 ml in the 5th, 6th, 7th, and 8th decades, respectively [45]. The rate of enlargement varies considerably at the individual level, but patients who have larger baseline volumes tend to experience a more rapid enlargement. Geographic variations in prostate size have also been found, with several studies showing significantly lower size in Asian men compared to North American and Australian men [46, 47]. Several authors have been able to demonstrate an increase in prostate size between age groups using either TRUS or pelvic magnetic resonance imaging [48, 49, 50, 51].

LUTS have also been demonstrated to increase with age, where numerous studies have described LUTS prevalence ranging from 15 to about 60 % in men in their 40s and 70s respectively [52, 53] [54]. Population based studies from Europe and North America have shown that the prevalence of moderate to severe symptoms was 13 % in men aged 40-49, increasing to 28 % in men older than 70 and rising to almost 50 % by the age of 80 years [53, 55, 56]. The aforementioned studies confirm the increasing prevalence of LUTS and BPH with ageing. However, the aetiology of BPH is still poorly understood.

Numerous mechanisms have been suggested and seem to be implicated in the pathogenesis of BPH. A decrease in prostate cell apoptosis has been shown in BPH, regulated by the inhibition of epithelial cell proliferation by tumour growth factor (TGF)- β [57]. Furthermore, the prostate gland is mainly composed by androgen-dependent tissue and dihydrotestosterone (DHT) is considered the androgen with the highest potency within the prostate because of its high affinity to androgen receptors. There is much evidence supporting the role of DHT in the pathogenesis of BPH. Development and growth of the prostate gland require the presence of testicular androgen during childhood, puberty and ageing and higher levels of serum DHT have been associated with an increased risk of BPH [58]. There are also findings suggesting that

estrogens could play a synergistic effect with androgens in the development of BPH [59]. Recently, the role of chronic inflammation has also emerged. Inflammatory cytokines, and particularly IL-8 was suggested as an association between chronic inflammation of the prostate and the growth of BPH [60]. Finally, the metabolic syndrome represents an well-known risk factor for the development of BPH by insulin resistance and secondary hyperinsulinaemia involvement, systemic inflammation and chronic oxidative stress [61].

1.6 PROGRESSION AND CONSEQUENCES

Numerous epidemiological studies and medical trials have brought forward strong evidence for the progressive nature of BPH. The Olmsted County study has shown that 31% of subjects have at least a three-point increase in IPSS over an eight-year period [62]. The Veterans Affairs study demonstrated that 36% of men with BPH allocated to watchful waiting needed invasive treatment within five years. The risk of suffering from an episode of acute urinary retention (AUR) was predicted as 23% for an average 60-year old man if he survived another 20 years [63].

Several risk factors have been identified for disease progression and the clinically most relevant one is prostate volume. Jacobsen et al, prospectively studied > 2000 men over four years and could show that an enlarged prostate > 30 mL was linked to a 3-fold risk, men with a peak flow < 12 mL/s had a 4-fold risk, and men with an IPSS of ≥ 8 had a 2.3-fold risk of suffering from urinary retention [64]. The requirement for surgery against BPH has been demonstrated to be strongly linked to age in previous studies [65, 66].

AUR is a devastating complication which can be a consequence of progressing BPH. Other precipitating causes include diabetes, neurologic disease, recent surgery especially with epidural or spinal anaesthesia and various medications, for example, tricyclic antidepressants or narcotics. Treatment consists of decompressing the bladder by catheterisation, followed by a trial without catheter (TWOC) a few days later, depending on the volume of retention. Adding an α -blocker has been shown to improve the chances of success of TWOC after AUR [67]. Failing a trial to void, a man should be recommended surgical therapy.

Chronic urinary retention (CUR) can be divided into high pressure and low pressure at urodynamic investigation where the former is vital to diagnose and relieve due to the increased risks of upper urinary tract dilatation and subsequent renal deterioration. CUR problems are best managed by clean intermittent self-catheterisation as opposed to long-term indwelling catheterisation, providing that the patient is a suitable candidate for such an intervention. Good manual dexterity and mental awareness are a prerequisite.

1.7 DIAGNOSTIC EVALUATION

The goal of the diagnostic work-up is to consider other possible diagnoses, other than BPH, related to prostatic enlargement, LUTS, or BOO. Once other causes have been excluded, the doctor should also evaluate whether BPH-associated complications have already occurred.

Medical history

A meticulous medical history is of paramount importance in the evaluation of patients seeking with LUTS and where the goal is to detect the possible causes and related comorbidities, as well as medical and neurological diseases. Additionally, present medication, previous surgery in the pelvic or spinal regions, lifestyle behaviors, emotional and psychological factors should be asked for. Focusing on the patient's perspective is essential and embraces comforting a man that there is no clear association between LUTS and carcinoma of the prostate [68, 69, 70].

Symptom score questionnaires

Every existing guideline for LUTS/BPH recommend using validated symptom score questionnaires [4, 5]. Questionnaires may aid in measuring the degree of LUTS and detecting which specific symptoms are most common; still, symptom scores are not age or disease specific. Symptom quantification is important to find out how severe the disease is, the progression of the disease over time, to identify the moment of necessary intervention, and to document the response to therapy. The International Prostate Symptom Score (IPSS) is now the international standard, developed by the AUA and described by Barry et al [71]. It is an eight-item questionnaire, consisting of seven symptom questions and one quality of life question. The IPSS is categorized as asymptomatic (0 points), mild symptoms (1-7 points), moderate symptoms (8-19 points), and severe symptoms (20-35 points). Restrictions include the inability to assess bother caused by each separate symptom, incontinence, and post-micturition symptoms. Furthermore, the IPSS cannot be used to reach the diagnosis of BPH. Patients with a many different dysfunctions of the lower urinary tract,

for example infections, tumours, neurogenic bladder disease, may also have an elevated IPSS. Finally, a symptom score alone does not represent the morbidity as felt by the individual patient. Treatment may make more sense for a man with moderate symptoms who finds them very bothersome than for a man with severe symptoms who finds them quite tolerable.

International prostate symptom score

Name:

Date:

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	

	None	1 time	2 times	3 times	4 times	5 times or more	Your score
Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	

Add Your scores and write total in the box to the right.

Total score: 0-7 Mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic.

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed: Equally satisfied / dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Figure 6. The International Prostate Symptom Score used to quantify LUTS

Frequency volume charts (FVC)

Noting the time and volume whenever an individual passes urine is denoted an FVC. Information that can be obtained from the FVC comprises day- and night-time amount of voids, total voided volume, the proportion of urine produced during the night, and amount of each void. Timing of the FVC should be long enough to evade sampling errors, but short enough to avoid non-compliance [72]. Previous reports have recommended that FVCs should continue for three or more days [73]. FVCs are useful to differentiate between frequency and nocturia due to bladder dysfunction, nocturnal polyuria, or increased fluid intake [74, 75]. In selected patients, FVCs may also be useful to document the severity of urgency and the timing of urinary incontinence.

Digital rectal examination (DRE)

DRE is used to judge prostate size, the consistency of prostate parenchyma for screening of prostate carcinoma, pain of the gland for exclusion of inflammation/infection, anal sphincter tone, and the rectal surface for exclusion of rectal carcinoma. Prostate volume tends to be underestimated with DRE and is as high as 25% in glands > 50 mL [76].

Urinalysis

Urinalysis must be part of the primary assessment of all LUTS patients in order to find diseases, for example a urinary tract infection or diabetes. General expert agreement suggests that the benefits of urinalysis offset the costs, even though the evidence is limited [77].

Prostate specific antigen

PSA is a glycoprotein produced by prostatic stromal cells, and is prostate- but not disease specific. Total serum PSA concentration may be elevated in the following circumstances: BPE, prostatitis, prostate carcinoma, prostate infarction, after ejaculation and immediately after prostate manipulation, for example DRE or prostatic biopsies. PSA can be used as a proxy measure of

prostate size where 1 gram of BPH tissue increases the PSA concentration by 0.3 ng/mL, in contrast to 1 gram of prostate cancer tissue that increases the PSA concentration by 3.5 ng/mL on average [78]. Serum PSA is a stronger predictor of prostate growth than prostate volume [51]. The PLESS study demonstrated that PSA can also predict alterations in symptoms, the degree of bother, and urinary flow-rate [79]. A study of men managed with conservative treatment, showed that PSA was an important predictor of clinical progression [80, 81]. From randomised controlled trials, it was shown that baseline serum PSA could predict the risk of suffering from acute urinary retention as well as requiring surgical intervention [66, 82]. A similar association was also seen in a longitudinal study where the risk for intervention was greater in patients with a baseline PSA of > 1.4 ng/mL [65].

PSA screening for prostate cancer in the general population is still controversial and therefore the potential benefits and harms of using PSA testing to look for prostate cancer amongst individuals with LUTS should be conversed with the patient [83]. The PSA-density (the serum PSA concentration divided by the prostate volume), PSA-velocity (increase over time) and the proportion of free to total serum PSA concentration can aid in the differentiation between BPH and prostate cancer.

Renal function measurement

Renal function can be measured using serum creatinine or estimated glomerular filtration rate. However, increased serum concentration of creatinine is only seen if more than 50% of the nephrons are damaged. Urinary retention, hydronephrosis or renal insufficiency are more common in men with signs or symptoms of BPO [84, 85]. Men having a reduced kidney function have an increased risk of suffering from post-operative complications [12].

Post-void residual of urine (PVR)

PVR of urine may be quantified by transabdominal ultrasound, bladder scanner or catheterisation. A high residual volume is not always linked to BPO, as high residual volumes can be secondary to obstruction and/or poor function of the detrusor muscle, for example detrusor underactivity [86]. The MTOPS and ALTESS studies, could demonstrate that high baseline residual

volumes were linked with an increased risk of symptom progression [66, 82]. It is possible to identify men who are at risk of going into AUR by monitoring changes of PVR over time. It is impossible to define a stringent PVR cutoff volume for decision-making purposes, due to the large patient variability. Volumes of 50-100 mL have been brought forward as a thinkable lower threshold to define abnormal PVR and values >300 mL are often used to identify men at risk of an unfavourable response following surgical intervention.

Uroflowmetry

Urinary flow rate assessment is a commonly used non-invasive urodynamic test. It is a screening test to assess and measure voiding at baseline and at follow-up. The main parameters are the maximum urinary flow rate (Q_{\max}) and the profile of the flow curve. Urinary flow rate is a product of the strength of the contraction of the detrusor muscle and the bladder outlet resistance. In men with dysfunctional voiding, uroflowmetry cannot discriminate between reduced contraction strength and increased bladder outlet resistance. The parameters of uroflowmetry should be assessed with voided volumes > 150 mL. A small amount of men with a $Q_{\max} > 15$ mL/s have BPO [87]. A $Q_{\max} < 11$ mL/s is associated with disease progression and those men have good chances to gain from medical or surgical treatment.

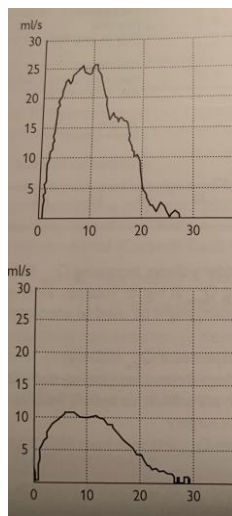


Figure 7. Examples of urinary flow curves in a normal adult (above) and in a man with suspected BPO (below).

Imaging

In routine clinical practice imaging of the prostate is usually performed by a transrectal ultrasound scan (TRUS) [88]. It is important to assess prostate size and architecture before selection of interventional treatment, for example, open simple prostatectomy, transurethral resection, enucleation techniques, transurethral incision of the prostate, or minimally invasive surgical therapies (MISTs). When considering treatment with 5α -reductase inhibitors it is helpful to know the size of the prostate. The volume of the prostate can predict symptom progression and the risk of complications. A median lobe may guide the choice of intervention men planned for minimally invasive method since the presence of a median lobe can be a contraindication for some MISTs.

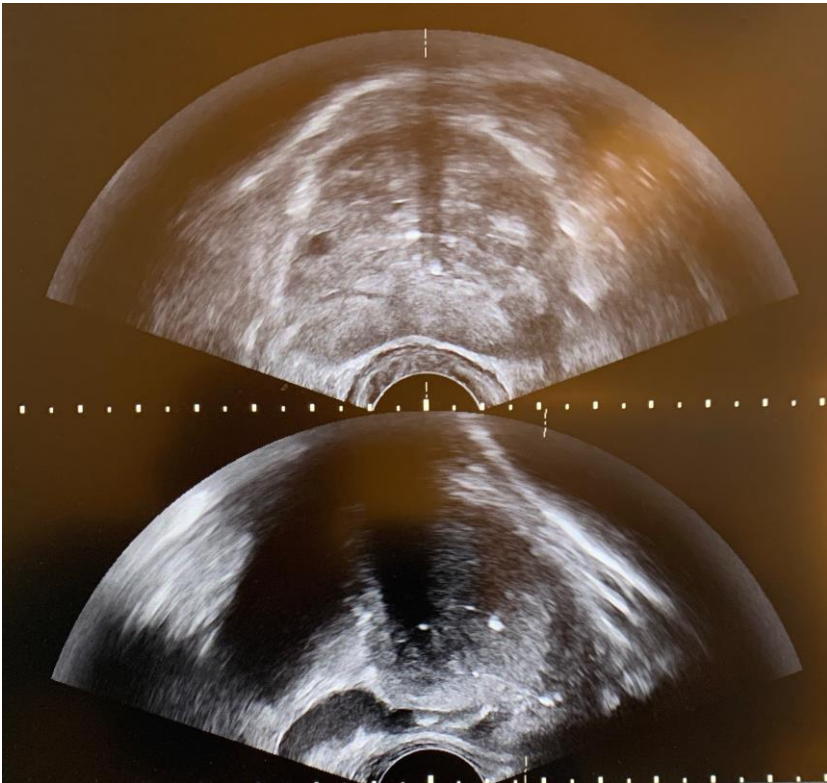


Figure 8. Transrectal ultrasound of the prostate gland in transverse (above) and sagittal (below) sections. Courtesy of Dr Nikolaos Galariotis.

Urethrocystoscopy

Although not an absolute necessity in the routine work-up, men having a history of macroscopic haematuria, stricture in the urethra, or bladder carcinoma, who seek with LUTS, must be examined with a urethrocystoscopy during diagnostic assessment.

Urodynamics

In men with LUTS, the most common techniques of invasive urodynamics are filling cystometry and pressure flow studies. The main aim of urodynamics is to assess the function of the lower urinary tract, to find risk factors for complications and to make data available to make the appropriate decision in treatment together with the patient. Pressure flow studies are needed to define BOO, which is characterised by an increased detrusor pressure and a decreased urinary flow rate during voiding. BOO must be distinguished from DUA, which is characterized by a decreased detrusor pressure during voiding together with a decreased urinary flow rate [34]. However, urodynamic evaluations are costly, time-consuming and may be associated with adverse events. The diagnostic profit, therefore, must be weighted against potential adverse events. Urodynamics is not necessary for the routine work-up of men with LUTS but recommended, by the European Association of Urology, before invasive treatment in men who: are unable to void > 150 mL, have a maximum urinary flow rate of ≥ 15 mL/s, are less than 50 or more than 80 years of age, can pass urine but still have a PVR > 300 mL, with suspected neurogenic bladder dysfunction, who have bilateral hydronephrosis, have had previous pelvic surgery or have undergone previous unrewarding prostate surgical intervention [4].

Non-invasive tests

Examples of non-invasive diagnostic testing include prostatic configuration/intravesical prostatic protrusion, thickness of the detrusor wall, ultrasound estimated bladder weight, and non-invasive pressure flow testing. Limitations concerning the diagnostic accuracy of these assessments are due to the variation and the small amount of reports of individual tests. The sensitivity, specificity, negative and positive predictive values from these tests were all very inconsistent [89].

1.8 WATCHFUL WAITING

Patients with mild to moderate symptoms who are not bothered and do not have any complicated factors should be offered watchful waiting. This regime includes patient education on BPE, BPH and BPO as well as reassuring them that they do not have cancer. Lifestyle advice should also be provided including reducing of fluid intake, avoiding caffeine and alcohol, encouraging double voiding, bladder retraining and treating constipation. The above measures were shown to improve symptoms and quality of life [90].

1.9 PHARMACOTHERAPY

α 1-adrenoreceptor antagonists (AAAs)

AAAs block endogenously released noradrenaline on smooth muscle cells in the prostate gland and as such reduces smooth muscle tone and outlet obstruction [91]. AAAs have, however, little effect on bladder outlet resistance, and therapy related improvement of LUTS is poorly linked with obstruction [92, 93]. AAAs exist in diverse preparations resulting in different pharmacokinetic and tolerability profiles. There is only a modest overall difference in clinical efficacy between the preparations. It takes a few weeks for the clinical effects to develop completely, but considerable efficacy over placebo may arise in a matter of days. AAAs are typically administered as the first-line medical therapy for men with LUTS due of their quick onset of action, fair efficacy, and little frequency and grade of side effects. Still, AAAs cannot prevent the occurrence of AUR or the need for surgical intervention [94, 95]. While AAAs are generally well tolerated, frequent side effects include asthenia, dizziness and orthostatic hypotension.

5 α -reductase inhibitors (5-ARIs)

The effects of androgen on the prostate gland are facilitated by dihydrotestosterone (DHT), which is converted from testosterone by the enzyme 5 α -reductase. This enzyme exists in 2 isoforms where type 2 is predominantly expressed and has its activity in the prostate. 5-ARIs bring about cell death of prostate epithelial cells causing a reduction in prostatic volume of almost 25% and a decrease in the levels of circulating PSA of almost 50% following treatment for at least 6-12 months [96]. During the equivalent time frame, the clinical effects of this medication can be seen. Following 2-4 years of treatment, 5-ARIs may improve IPSS by about 2 points and increase Q_{\max} by 2 mL/s in patients with LUTS due to BPE. 5-ARIs can reduce the long-term risk of going into AUR or requiring surgical intervention [97]. Additionally, 5-ARIs could decrease bleeding during transurethral resection of the prostate, possibly due to its effects on the vascular supply to the prostate [98]. Commonly encountered side effects include erectile dysfunction and reduced libido. Prescription of 5-ARIs should be considered in patients having moderate LUTS as well as a prostate >40 mL and/or an elevated PSA >1.5 ng/mL. 5-ARIs are not appropriate for

short-term use due to the slow onset of action and their effect on the PSA level should be considered in relation to prostate cancer screening [89].

Combination therapy

Combination therapy most commonly consists of an AAA together with a 5-ARI. Four-year data seen in the CombAT and MTOPS studies demonstrated that combination therapy is better to monotherapy for symptoms and urinary flow rate and also in preventing disease progression [66, 95]. Yet, combination therapy can also be accompanied by a higher incidence of side effects. Combination treatment should be administered primarily in patients who have moderate symptoms and are at risk of disease progression, for example, a higher PSA concentration, a higher prostate volume, advanced age, low urinary flow rates, and higher residual volumes, [89]. It should only be prescribed when long-term therapy is intended which requires a high patient compliance.

Muscarinic receptor antagonists

Innervation of the bladder muscle is through parasympathetic nerves whose key neurotransmitter is acetylcholine, that stimulates muscarinic receptors on the smooth muscle cells. Antimuscaric drugs may substantially improve urgency, UUI, and increased daytime frequency [99, 100]. They can be associated with increased PVR after therapy and should therefore be prescribed with some caution [101]. Men should be recommended to stop medication if symptoms get worse or a weaker urinary stream is noted after commencement. Side effects include dry mouth, voiding difficulties, nasopharyngitis, constipation, and dizziness.

Phosphodiesterase inhibitors (PDE5Is)

PDE5Is increase intracellular cyclic guanosine monophosphate, thereby reducing the tone of smooth muscle of the detrusor, prostate and urethra [102]. PDE5Is were originally introduced for the treatment of erectile dysfunction. A recent Cochrane review showed that PDE5Is improve IPSS, storage and voiding LUTS, and reduce the degree of bother, although the

effects are minimal [103]. Reported adverse effects include flushing, gastroesophageal reflux and headache.

Beta-3 agonists (B3As)

The β_3 receptor is the main beta-receptor expressed in the smooth muscle cells of the detrusor and its stimulation brings about relaxation of the detrusor muscle [106]. B3As improve symptoms of overactive bladder, including urgency, voiding frequency, and urge urinary incontinence [107]. The most common adverse events are hypertension, UTI and headache.

Phytotherapy

Preparations consisting of herbal drugs come from of roots, pollen, seeds, fruit, or bark. One capsule may contain preparations from a single plant or a combination of two or more plants preparations [104]. Variation and a limited regulatory framework illustrate the present status of phytotherapeutic drugs. A Committee on Herbal Medicinal Products has been developed by The European Medicines Agency which currently only recommends *Serenoa repens* for routine use [105].

1.10 TRANSURETHRAL RESECTION OF THE PROSTATE (TURP)

Monopolar TURP (M-TURP)

M-TURP removes tissue from the transition zone of the gland and is an effective treatment for bothersome LUTS secondary to BPO. It is considered the gold standard procedure for patients with prostate volumes between 30 – 80 mL. The upper volume limit for the procedure is advised as 80 - 100 mL, because as the time of operation gets longer, there is a considerable rise in the incidence of adverse events and the operation is safest when completed < 90 minutes [108].

TURP is generally performed under general or spinal anesthesia. Removal of the obstructing tissue of BPH from inside the prostatic urethra, leaving the surgical capsule intact. A metallic wire loop, which is electrically heated is used through a resectoscope, to cut the prostatic tissue and coagulate bleeding vessels (Figures 9 & 10) [109]. Through the continuous flow of irrigating fluid the cut bits of tissue are pushed back into the bladder and at the end of the procedure they are evacuated using specially designed instruments.

The absolute indications for TURP are:

- Bothersome LUTS that fail to respond to lifestyle changes or pharmacotherapy
- Recurrent AUR
- Impairment of renal function due to BOO
- Recurrent haematuria due to BPE
- Stones in the bladder due to BPO
- Recurrent urinary tract infections

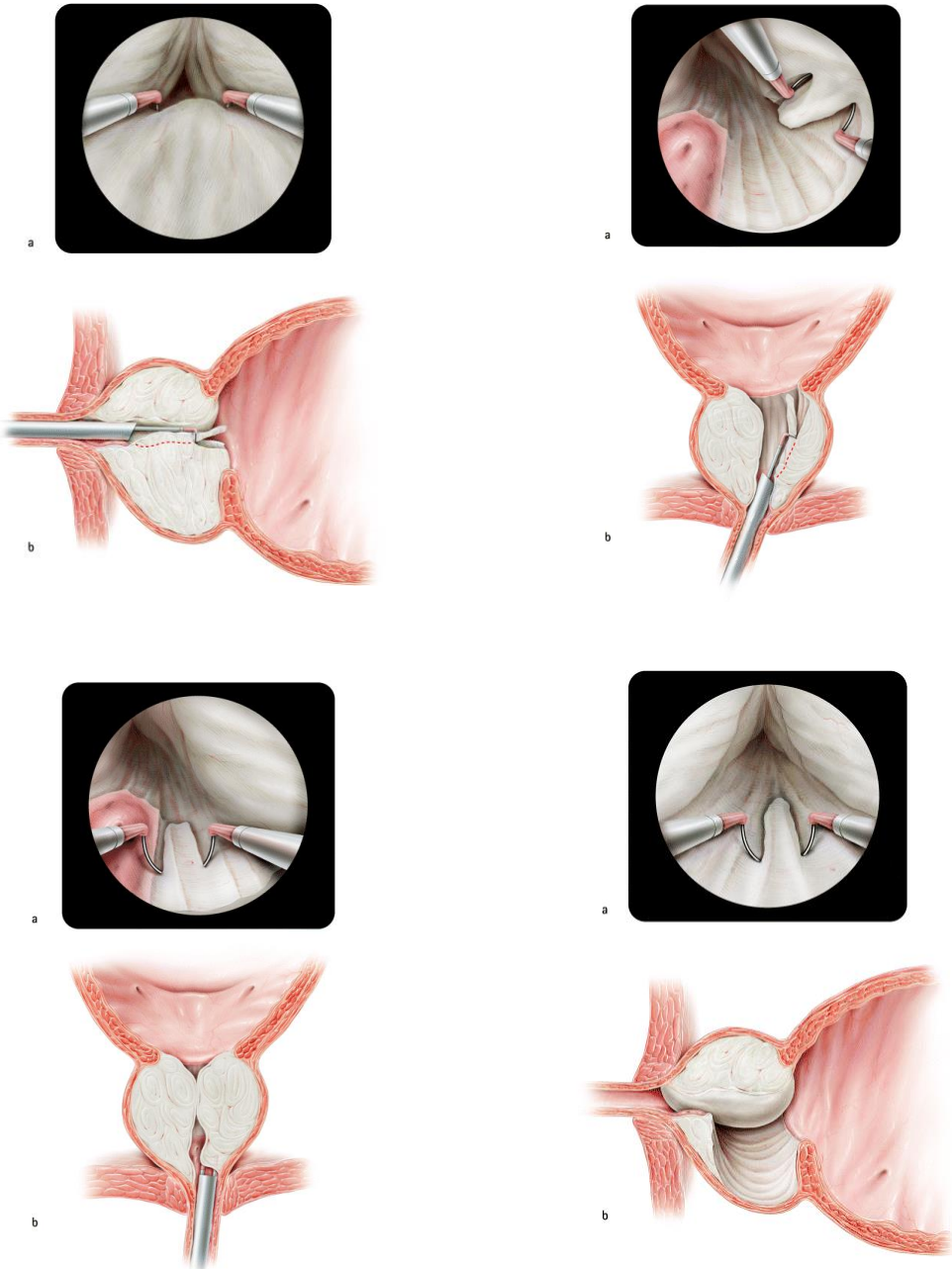


Figure 9. The surgical steps during TURP. From May F, Hartung R. Surgical atlas. Transurethral resection of the prostate. *BJU Int*, 2006;98(4):921-34. Permission granted.

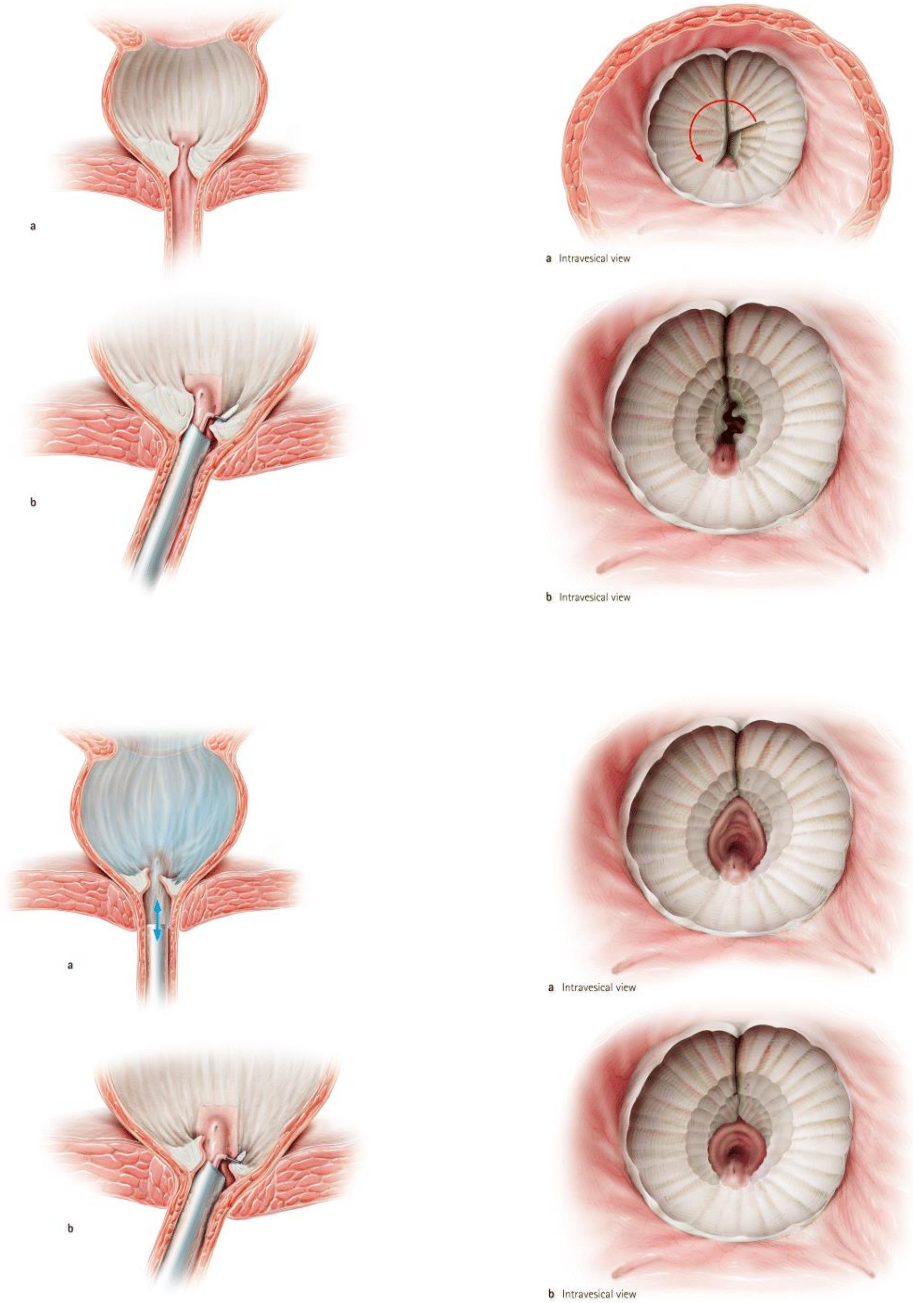


Figure 10. The surgical steps during TURP. From May F, Hartung R. Surgical atlas. Transurethral resection of the prostate. *BJU Int*, 2006;98(4):921-34. Permission granted.

Complications associated with a TURP procedure

Peri-operative morbidity and mortality and have gradually improved over the decades, even though the former still remains significant at 0.1% and 11%, respectively [13]. The risk of TUR syndrome has decreased to < 1% [14]. The risk of profound bleeding requiring transfusion is about 3%, AUR is 5%, clot retention requiring surgical evacuation is 5% and UTI is 4% [15]. Long-term complications include permanent urinary incontinence, recurrent urinary retention, contracture of the bladder neck, stricture of the urethra, retrograde ejaculation and erectile dysfunction [110]. These complications have not been studied in a structured way using uniformly comparable methods and therefore the precise incidences are difficult to quantify. This also applies for the postoperative risks of developing an acute myocardial infarction, a deep vein thrombosis or a pulmonary embolism.

The feared TUR syndrome is an uncommon complication but is important to recognise since it can potentially be life-threatening. It happens because of irrigating fluid being absorbed into the venous sinuses of the prostate. The signs and symptoms of TUR syndrome are often vague and unspecific but may include confusion, headache, nausea, visual disturbances, bradycardia and tachypnoea. The operating surgeon needs to have a high index of suspicion of this complication which is mainly treated by supportive care if the diagnosis is made early and management is started before systemic complications occur, for example cerebral oedema, convulsions and pulmonary oedema. These men need monitoring in an intensive care unit.

1.11 ALTERNATIVE SURGICAL METHODS

Bipolar TURP

B-TURP allows for the procedure to be conducted using normal saline as irrigating fluid. As opposed to the conventional monopolar method, energy does not pass through the patient to reach a skin pad in B-TURP. The electric circuit of this system is completed locally; energy is kept between an active resection loop and a passive pole located on the tip or the sheath of the resectoscope [111, 112]. Otherwise, the removal of prostatic tissue is similar to the monopolar method.

B-TURP is the alternative procedure that has been studied most extensively compared to M-TURP. In randomised trials, data with 5-year follow-up showed no difference in functional outcomes [113]. B-TURP may be desirable because of a more favourable peri-operative safety profile, for example, the avoidance of TUR syndrome, decreased rates of clot retention and blood transfusion, shorter irrigation time, catheterisation time and probably hospitalisation time [113, 114].

TUIP

Transurethral incision of the prostate is recommended for prostate glands < 30 mL in size. It is by some urologists seen as an underused technique as it has shown comparable efficacy with relatively low morbidity compared to TURP. However, re-intervention rates remain high.

Open simple prostatectomy (OP)

OP is the eldest surgical intervention for bothersome LUTS caused by BPE. The enlarged tissue that obstruct the prostatic urethra are enucleated using the index finger, approaching transvesically from within the bladder (Fuller/Freyer procedure) or retropubically through the anterior prostatic capsule (Millin procedure). OP is the most invasive surgical procedure, but it is efficacious and long-lasting treatment method for symptoms associated

with BPE [115]. OP is the surgical intervention of choice for men with prostate volumes > 80-100 mL but might also be contemplated in smaller prostates in other parts of the world where endourological are not readily available.

Transurethral microwave thermotherapy (TUMT)

The TUMT procedure is performed as an outpatient procedure under local anaesthesia using a catheter that is inserted in the urethra. This catheter contains an antenna that produces high-energy microwaves and an intraprostatic probe, which measures temperatures in the prostate gland during the procedure. Treatment times vary between 6-15 minutes depending on the size of the prostate and a man can normally go home directly after the procedure is finished. After 5-year follow-up, functional outcomes seem similar to TURP but with a more favourable safety profile [116, 117, 118].

Laser enucleation/resection (ThuVEP/ThuLEP/ThuVARP)

The thulium:yttrium-aluminium garnet (Tm:YAG) laser, emits wavelengths between 1940 and 2013 nm in a continuous mode. Different applications, ranging from vaporisation, enucleation and vaporesction have been produced and studied. There is a need for continuing investigation of the efficacy of these techniques since there are only a few trials with long-term follow-up supporting their routine use [119, 120, 121].

Diode laser vaporisation/enucleation

Diode laser vaporisation leads to comparable improvements in functional outcomes during short-term follow-up and offers decent properties of haemostasis. Diode laser enucleation appears to lead to comparable safety and efficacy when compared to either transurethral resection or bipolar enucleation of the prostate. With only a limited number, and quality of RCTs, coupled with debatable data on the re-intervention rate, results for diode laser vaporisation and enucleation need to be assessed in future studies of better quality [122, 123, 124, 125].

KTP lasers

The potassium-titanyl-phosphate (KTP) laser works in the blue-green to green spectrum at 532 nm. The energy is absorbed by molecules of haemoglobin but not by water. Prostatic tissue is immediately removed through vaporisation. Compared to TURP the KTP laser demonstrates higher intra-operative safety with regard to haemostasis. The time of catheterisation and hospital stay favours KTP, while the operation time and the risk of a re-intervention favour TURP [126]. The KTP laser appears to be safe for the treatment of men using antiplatelet or anticoagulant therapy, though, the evidence level is low [127].

HoLEP laser enucleation

The holmium:yttrium-aluminium garnet (Ho:YAG) laser is a pulsed solid state laser that is absorbed water containing tissues. The coagulation and necrosis of tissue are restricted to 4 mm which is sufficient to obtain acceptable haemostasis. HoLEP necessitates relevant endoscopic skills and surgical experience, with the latter being the most significant factor affecting overall occurrence of complications [128]. Laser enucleation of the prostate has shown better safety profiles, for example haemostasis, when compared to OP and TURP [129, 130]. The duration of postoperative catheterisation and stay in the hospital are in favour of HoLEP [131]. Over a long timeframe functional outcomes of HoLEP are similar to OP [132].

Water vapour energy ablation (Rezum system)

This method uses radiofrequency power creating thermal energy using water vapour, which in turn delivers the deposited thermal energy when the steam phase changes to liquid upon cell contact. The steam scatters throughout the tissue interstices and delivers stored thermal energy onto prostatic tissue leading to apoptosis. Treatment can be carried out as an outpatient procedure.

Compared to sham treatment, using rigid cystoscopy with imitated treatment sounds, Rezum showed improved IPSS, QoL and Q_{\max} after 4-years follow-up [133]. The method shows a relatively favourable safety profile with mild

to moderate adverse events. Preservation of erectile and ejaculatory function has also been demonstrated. This method is still under investigation and needs to be tested against the reference technique of TURP to confirm the first promising results.

Robot-assisted simple prostatectomy (RASP)

RASP appears equivalent to OP when it comes to efficacy and safety, demonstrating comparable improvements in voiding parameters and symptom scores. Most studies are, however, of a retrospective nature [134, 135] and there is a call for studies of higher quality in order to compare the efficacy, safety and hospitalisation times of RASP against both OP and endoscopic interventions. Long-term functional outcomes, the learning curve and the costs of RASP also need to be evaluated.

Prostatic artery embolization (PAE)

PAE can be conducted under local anaesthesia with vascular access through the femoral or radial arteries. Digital subtraction angiography shows the anatomy of the arterial tree and the suitable prostatic vascular supply is selectively embolised creating stasis in the treated vessels. The technical approach may encounter anatomical obstacles, for example, atherosclerosis, excessive arterial tortuosity, and the presence of adverse collaterals [136]. An approach encompassing a multidisciplinary is required and selection of the appropriate candidate should be carried out by urologists and interventional radiologists. Men with larger prostates (>80 mL) possibly have the most to gain from PAE. This intervention is less effective than TURP at improving LUTS and voiding outcomes like urinary flow rate [137]. Compared to transurethral resection, the treatment time is longer in PAE, although haemostasis, catheterisation time and hospitalisation time are in favour of this novel method that remains under investigation.

Prostatic urethral lift (PUL)

PUL is a new minimally invasive method that can be carried out under local or general anaesthesia. The intruding lateral lobes are compressed by small permanent suture-based implants that are delivered under guidance by a rigid cystoscope and leads to a widening of the lumen in the prostatic part of the urethra. This creates a continuous anterior channel throughout the fossa of the prostate starting from the bladder neck and extending to the verumontanum. Generally, PUL achieves a considerable improvement in symptom scores, quality of life and urinary flow as compared to a mock procedure [138]. However, the improvements concerning functional outcomes are inferior to TURP after two years [139]. Additionally, a protruding and obstructing lobus tertius cannot be effectively treated, and the efficacy in large glands has not yet been demonstrated. An advantage of this technique is that it appears to have no substantial negative impact on sexual function. The most common adverse events seen post-operatively are, dysuria, pelvic pain, haematuria urgency, temporary incontinence, and UTI [140].

2 AIMS OF THE THESIS

The overall aim of this thesis was to explore and elucidate the effects of monopolar transurethral resection, in a non-academic setting, on men suffering from LUTS or urinary retention due to BPE. The specific aims of each paper were as follows:

Paper I

To investigate the response rate regarding objective and subjective voiding outcomes following a TURP procedure in two distinctly different patient categories; men with bothersome LUTS and men in urinary retention requiring catheterization.

Paper II

To disclose the frequency and severity of peri- and post-operative complications associated with a TURP procedure.

Paper III

To analyze patients defined as non-responders after a TURP procedure in our department with the principal aim to reveal their fate.

Paper IV

To disclose an economic evaluation of in-hospital costs associated with a TURP procedure as well as to determine the predictors of differences in total cost.

3 PATIENTS AND METHODS

3.1 ETHICAL CONSIDERATIONS

Ethical approval were granted for **Papers I-III** (Dnr 202-15) and for **Paper IV** (Dnr 2020-02647) by the regional ethical committee at the University of Gothenburg.

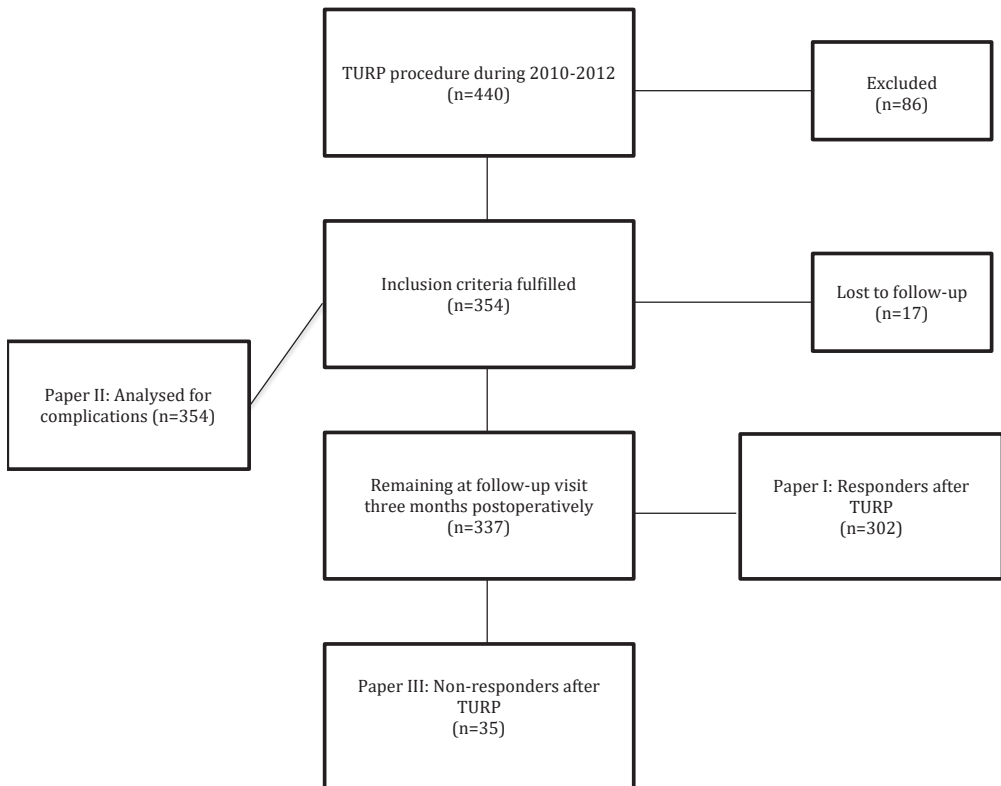
All patients underwent preoperative work-up and peri-operative care according to the local routines of the Department of Urology at Skaraborgs Hospital applicable to the time frames of 2010-2012 and 2017-2019 respectively. No additional work-up or perioperative care was carried out on the study subjects.

3.2 PATIENT COHORTS

The study subjects of **Papers I-III** consisted of a cohort of 440 sequentially enlisted individuals subjected to a TURP procedure at Skaraborgs Hospital in Sweden between 2010 and 2012. Please see the study flow chart for further details (Figure 11). Inclusion criteria were benign prostatic enlargement demanding surgical intervention, either because of troublesome LUTS or due to urinary retention necessitating an indwelling catheter or clean intermittent self-catheterisation (CISC). Exclusion criteria were a previously performed transurethral intervention on the prostate as well as apparent prostate or bladder cancer before the procedure.

In **Paper IV** we retrospectively analysed a cohort of 122 men subjected to a TURP procedure at Skaraborgs Hospital in Sweden during the time frame January 2017 until December 2019 by gathering hospital expense data from in-patient care expenses from the Department of Urology. The data were generated by the electronic hospital accounts management system and presented in an Excel® file format. The Diagnoses Codes of N40.9 (Benign Prostatic Hyperplasia) and R33.9 (Urinary retention,) in The International Classification of Diseases, 10th revision (ICD 10), were used for the search in combination with the surgical procedure TURP (operation code KED22).

Figure 11. Flow-chart of the study subjects in Papers I-III



3.3 THE SURGICAL PROCEDURE

The operations were conducted using a Charrière 26 monopolar resectoscope from Storz with an Erbe V10 300 generator (Tübingen, Germany) set at 180W cutting and 80W coagulation mode (dry cut). All resections were performed using standard loops and irrigating fluid containing sorbitol-mannitol 3% solution (Braun, Germany). Medical therapy with anticoagulants or platelet aggregation inhibitors was stopped before surgery. Men with a preoperative negative urine culture were provided with a single prophylactic dose of an antibiotic where as men with an indwelling catheter and/or a positive urine culture were treated against infection for ten days commencing the day before surgery. In **Papers I-III**, 13 urological surgeons of whom six were residents-in-training carried out the interventions. In **Paper IV**, the operations were performed by 14 urological surgeons, including eight residents-in-training.

Postoperatively a Charrière 22 three-way catheter was inserted, and irrigation of the bladder was started with normal saline solution. A trial without a catheter (TWOC) was normally started on the first postoperative day whereby the patient was encouraged to pass urine. In **Papers I-III**, if this trial failed up to a maximum of three attempts during the following days a man was discharged with an indwelling catheter and came back to the ward for a new attempt two weeks later. In **Paper IV**, if this trial failed up to a maximum of two attempts during the following days a man was discharged with an indwelling catheter and with instructions of TWOC given to primary care.

3.4 COLLECTED VARIABLES

In **Papers I-III**, baseline characteristics collected before surgery included patient age, body mass index (BMI), American society of anaesthesiologists' classification (ASA), transrectal ultrasound volume of the prostate (TRUS), prostate specific antigen level (PSA), peak urinary flow rate (Q_{\max}), post-void residual (PVR) volume, International Prostate Symptom Score (IPSS) and bother score (BS). The final question on the IPSS questionnaire was used to determine the bother score (graded 0-6). The presence of CISC or an indwelling catheter was also noted. Perioperative variables included anaesthesia type, duration of surgery, surgeon category, weight of resected tissue, blood loss, postoperative catheter drainage time and duration of hospital stay. Hospital stay was calculated, in days, from time of operation end until time of discharge from hospital. The TRUS volume of the prostate gland was calculated using the prolate ellipse volume method (height x length x width x $\pi/6$). The PVR was measured by a BladderScan® (Allytec, Sweden).

Preoperative demographic variables of BMI and ASA grade provided an indication on the morbidity of the study population. To assess voiding parameters, we used the objective parameters of Q_{\max} and PVR, as well as the subjective parameters of IPSS and bother score, as these are the most established methods used in similar studies. Blood loss was assessed using the Low Haemoglobin System (HemoCue, Ängelholm, Sweden) in each bucket of collected irrigating fluid [141].

Outcome variables, used for **Papers I and III** including Q_{\max} , PVR, IPSS and bother score were registered at a nurse-led clinic 3 months postoperatively. Histological examination of resected specimens was as a rule performed discretionally by the operating surgeon. After this visit the sequential follow-up of each patient, analysed in **Paper III**, was individualised at the discretion of the urologist in charge. No formalised follow-up schedule was used. The non-responders were followed in detail using retrospective chart reviews from hospital records. The follow-up was discontinued after a maximum time of three years or when symptoms and flow rate had improved, and patients were satisfied with their current state of voiding.

In **Paper IV**, data included items such as patient age, length of hospital stay, specific costs for anaesthesia, laboratory testing, pathology reports, medication use, treating staff, interventional equipment and the cost for occupying a hospital bed. The calculations of the expenses from interventions

and surgical facilities were founded on mean personnel costs per minute, fixed charges for facilities, and devaluation of equipment. The costs for a TURP procedure encompassed the average salary of the urological surgeon, costs for operation facilities including premises, equipment, and technical staff. The cost of medical supplies needed for the operation included the resection loop, irrigation solution, and tissue evacuation system. Costs for anaesthesia included the anaesthesiology staff and its accompanying medical supplies. Costs for the histological examination of the resected tissue were also noted. Costs for the inpatient stay included the doctor's average salary, patient care by specialist nurses, medical supplies including irrigation fluids and perioperative care, medications, laboratory services, administration and accommodation (housekeeping, catering and premises). The latter was based on fixed amounts calculated by the department of accounting.

Prices were recorded as the amounts from the National Board of Health and Welfare in Sweden founded on diagnosis related groups (DRG). This is a system used to categorise in-hospital cases into original groups, depending on the severity of illness, prognosis, the difficulty of treatment, and the intensity of resources utilised. The system is used in several European countries to assign for example any in-patient stay into groups for the purpose of payment and reimbursement. In Sweden, separate pricelists were identified for subjects with or without minor comorbidity and for subjects with major comorbidities. In this study complete datasets including all patients with a first hospitalisation for the DRG code of N05N was obtained.

We included all costs occurring during the period of stay of in-patient care for a TURP procedure including any peri- or postoperative complications occurring during in-hospital care. Costs of outpatient visits, emergency department visits, readmissions to the urology ward and visits to general practice were not included in this study. The costs are reported in Swedish Krona (SEK) and were transformed to Euros (€), as a more commonly used currency, based on the exchange rate as of 24th June 2020 (1 SEK = 0.09 €). All costs exclude value added tax.

3.5 DEFINITION OF OUTCOME VARIABLES

Responders versus non-responders

Following modified de Wildt outcome criteria [142], responders were defined as those with:

- an IPSS of ≤ 7 or more than a 50% loss as compared to baseline
- a Q_{\max} of ≥ 15 mL/s or more than a 50% gain as compared to baseline
- a PVR of ≤ 100 mL
- and/or a bother score of ≤ 2

Subjects achieving at least one out of the four criteria were judged to be responders. Subjects achieving none of these criteria were consequently judged to be non-responders. A response in men suffering from urinary retention, requiring an indwelling catheter or needing CISC was judged as being catheter-free at 3 months follow-up.

Grading of postoperative complications

Complications were grouped and evaluated into three subcategories; (1) hospital stay, (2) the timeframe between discharge from hospital and the follow-up visit three months later and (3) any late endourological re-interventions happening within five years from the first procedure. Complications were defined and graded following the Clavien-Dindo (CD) system [143, 144, 145]. Please see **Paper II** for a detailed description of the CD system.

In our study, CD grades I and II were predefined as mild to moderate complications and CD grades \geq III as major complications. Treatment of an assumed and/or a established UTI with either oral or intravenous antibiotics, during hospital stay or treated with oral antibiotics by a doctor in primary care after discharge and until follow-up, was defined as a CD grade II complication.

3.6 STATISTICAL ANALYSIS

Papers I-III

Median numbers together with the interquartile range (IQR) were presented as descriptive statistics for continuous variables as most of them were of ordinal data type and/or did not follow a pattern of normal distribution. For categorical variables frequencies and percentages were presented. A p-value < 0.05 was considered statistically significant. All data were analyzed using SPSS version 22.0 (Inc, Chicago, IL).

Paper IV

A detailed methodological description on the statistical methods used to analyse the costs associated with a TURP procedure is provided in the manuscript of Paper IV.

3.7 METHODOLOGICAL CONSIDERATIONS

Paper I

We decided to divide our study cohort into, two distinctly different groups of patients who had been subjected to a TURP procedure: men with bothersome LUTS and men with problems of urinary retention. The group with urinary retention included men with an indwelling catheter but also men utilizing clean intermittent self-catheterisation. We found this distinction important since the function of the lower urinary tract in these two groups are most probably different and they should therefore not be compared directly against one another.

This was an observational cohort study with little loss to follow-up (5%) and, hence, the internal validity of the study was judged to be good. The main limitation was the relatively high proportion of missing data in the functional outcome variables. Despite our efforts it was not always feasible to conduct a uroflowmetry for every follow-up subject. Patient compliance with filling out the IPSS was also problem. Our relatively short follow-up interval of three months did probably not reflect a fair analysis on post-operative functional outcomes. However, unlike most other hospitals in Sweden, during the time frame of 2010-2012, we did still have a formal follow-up schedule, at a nurse-led clinic, for these men. This routine provided valuable information which enabled our studies. The surgical procedure was performed at a single site by a group of urological surgeons with varying surgical experience, which can be a limitation of this study. There most probably was a selection bias of men with large prostates operated on by experienced surgeons which might have had an influence on postoperative voiding outcomes. However, our findings should be seen to mirror the realities of routine clinical care.

Paper II

Following the world-wide accepted recommendations of using the validated Clavien-Dindo system of grading postoperative complications we grouped complications into immediate, early and late complications. However, we were not able to capture any contingent complications that might have lead a man to seek the primary care setting or another hospital outside our own catchment area. Furthermore, we did not formally analyse the effect TURP

might have had on erectile function and ejaculation. Finally, our multivariate logistic regression model should be interpreted with caution as we included too many predictive variables in relation to a dichotomous outcome variable with relatively few occurrences.

Paper III

In this paper we retrospectively looked at a small cohort of patients using medical records. This is a clear limitation of this study and therefore it is difficult to come to any generalisable conclusions. Nevertheless, we have in a detailed manner investigated the fate of all non-responders from a routine setting and with a long follow-up time, which can also be a strength.

We used clear but somewhat stringent criteria when defining a response after a TURP procedure. A non-responder, in the LUTS group, was defined as man with all postoperative parameters as follows: an IPSS > 7 , a bother score > 2 , a Qmax of < 15 mL/s and a PVR > 100 mL. This can of course be questioned and illustrates the difficulties in defining a failed response after a surgical intervention for BPE. Furthermore, in the men with urinary retention, a non-responder was defined as a man still requiring CISC or an indwelling catheter postoperatively. However, a man who went from being chronically catheterized to using CISC with intermittent voiding might very well be pleased with the postoperative result and as such should have been regarded as a responder.

Paper IV

This retrospective study, using patient chart reviews, has certain limitations and our findings should therefore be interpreted with some caution. For example, costs of complications occurring after discharge from hospital such as emergency department presentations with acute urinary retention, macroscopic haematuria or septicaemia or visits to the GPs office due to urinary tract infection were not included. Moreover, the costs associated with readmission to the Urology ward for any reason is not included. This needs to be accounted for when comparing different treatment modalities against each another. Furthermore, the true cost of an intervention requires a holistic approach and can be divided into direct costs (of drugs, operations, consultations and complications), indirect costs (lost earnings due to sick leave) and intangible costs (pain and suffering). In this analysis, we have only studied the direct costs. We did, however, include all costs incurred during the in-hospital stay, including costs of complications after TURP associated with a prolonged length of stay. In addition, we have provided a detailed

economic analysis using in-hospital data from the hospital financial department from a recent time period (2017-2019). This possibility did not exist for the older patient cohort (2010-2012) as the financial in-hospital data from that time period was not as extensive and detailed as only modern upgraded systems are able to provide.

4 RESULTS

4.1 PAPER I

Men subjected to a TURP procedure in this study were derived from 181 men with bothersome LUTS and 156 men with problems of urinary retention (UR). The median age in the two categories of men were 68 years and 72 years, respectively. Median prostate volumes were 50 cc and 53 cc, respectively. Men with bothersome LUTS had poor preoperative voiding function exhibiting a median urinary flow of 7,6 ml/s, a median residual urine volume of 100 ml, and median values of IPSS and bother score of 21 and 4, respectively. The vast majority of men had mild to moderate comorbidities as judged by ASA grade. For further details please find a table on patient demographics in **Paper I**.

The median operating times were 61 minutes and 67 minutes in the LUTS and the UR groups, respectively. The median resection weights were 20 grams and 27 grams and the resection speed was 0,33 g/min and 0,42 g/min, respectively. The postoperative catheter duration was 19 hours and 18 hours, respectively and the median hospital stay was 2 days in both groups. Upon discharge 92% and 77% of men were catheter-free. A table on detailed perioperative variables can be found in **Paper I**.

Of the 181 men with bothersome LUTS, the median IPSS decreased from 21 pre-operatively to 7 post-operatively, the Q_{\max} increased from 7.6 to 13.2 mL/s, the PVR decreased from 100 to 20 mL and the bother score from 4 to 2. A total response rate of 95% was calculated and 25% of the men came out as excellent responders, achieving all predefined outcome criteria. Of the 156 men with UR, 77% could be sent home without a catheter and 83% were subsequently catheter-free at follow-up three months later and were defined to be responders, accordingly. Of the 17% non-responders, who still needed a catheter at three months after a TURP procedure, the vast majority used CISC and only six needed an indwelling catheter. Detailed results on the functional voiding outcomes of these men can be found in **Paper I**.

4.2 PAPER II

The patient demographics of the 354 men included in this study can in detail be seen in **Paper II**. The median age and prostate volume were 70 years and 50 cc, respectively. The median preoperative voiding parameters were as follows: an IPSS of 20, a bother score of 4, a urinary flow rate of 7,4 ml/s, and a residual urine volume of 185. Most men had a mild or moderate comorbidity status with only 17% having ASA grades of III or above.

Complications occurring during hospital stay were in the majority of cases of mild to moderate nature. The percentages of Clavien-Dindo grades I-IV were as follows: CD I: 18%, CD II: 10%, CD IIIa: 1,1%, CD IIIb: 0,8% and CD IVa: (0,6%). No patient had a CD IVb or CD V complication during hospital stay. For detailed descriptions on the frequencies and types of complications please see **Paper II**.

Complications occurring after discharge from hospital and until the scheduled follow-up three months later showed a similar pattern with most cases being mild to moderate in nature. The percentages of Clavien-Dindo grades I-IV were as follows: CD I: 11%, CD II: 13%, CD IIIa: 1,4%, CD IIIb: 1,1%, CD IVa: (0,6%), and CD V: 0,3%. No patient had a CD IVb complication during this time frame. For detailed descriptions on the frequencies and types of complications please see **Paper II**.

4.3 PAPER III

In this study we identified 35 men judged to be non-responders after a TURP from our first study in Paper I. This group of non-responders was made up of nine men who underwent surgery because of bothersome LUTS and 26 men who underwent surgery because of problems with urinary retention. All 35 men were seen by a specialist nurse at 3 months and subsequently followed for a mean time of 11 months by retrospectively examining their patient records. Further diagnostic investigations were undertaken in all men where the specific pathway was up to the specific urologist in charge. Endourological re-interventions were carried out in a total of nine men, with redo-TURP undertaken in seven cases and incision of the bladder neck in two cases. For further details on the fate of each non-responder please see the figures presented in **Paper III**.

4.4 PAPER IV

A total of 122 subjects were available for final analysis. Background and perioperative variables as well as costs categorised into specific expense items are presented in the manuscript version of **Paper IV**. The main expense items were, in order of median cost per person, surgical procedure, in-patient care, anaesthesia and recovery unit care, respectively. The variation of costs specified for in-patient care and recovery unit were considerable and overall, the recovery unit exhibited greater costs than anaesthesia. The minor expense item, in order of median cost per person, comprised costs for histopathological analysis, the starting cost, transfusion lab costs, clinical physiology, microbiology lab costs, medications and, finally, laboratory services.

The vast majority of costs at the transfusion laboratory services were for Group, Save and Cross-match of blood preoperatively. Only 3% of the subjects demanded a blood transfusion postoperatively, mirroring the costs for this item. Costs in the microbiology department were mainly due to perioperative urine cultures and in a few cases due to blood cultures in cases of suspected septicaemia. In all, 5% of men received postoperative treatment with intravenous antibiotics due to febrile urinary tract infections.

In uni- and multivariable analysis of pre- and perioperative variables total cost was positively associated with patient age, prostate volume and the presence of urinary retention preoperatively. The adjusted R^2 values were low, indicating a modest correlation. In a univariable analysis, total cost was strongly positively associated with the postoperative catheter time, in the length of stay at the hospital and the occurrence of postoperative complications.

For further details on results from this study please see the attached manuscript of **Paper IV**.

5 GENERAL DISCUSSION

Transurethral resection of the prostate (TURP) is a surgical procedure that has, since long, been a remedy for benign prostate enlargement. The literature is generously endowed with reports on favourable outcome, reasonably low complication rates and this to a comparatively low cost. These reports, however, are mostly derived from data from tertiary referral centers and university hospitals. The Swedish Council on Health Technology Assessment particularly pointed out the need for reports from non-academic centers. They asked for information on various aspects of TURP surgery not only encompassing clinical outcome, complication rate, and the outcome of redo surgery. They also called for a comprehensive and candid presentation on costs in a real-world setting at a non-university hospital. Prompted by these wishes, we set out on a journey with the aim to shed some light over these questions.

According to our findings, a man subjected to a TURP having either LUTS or UR ended up with a satisfactory outcome in the majority of cases. And, moreover, the vast majority of men could void spontaneously at follow-up a quarter of a year later. Not surprisingly, men who, prior to surgery, were in retention had a catheter-free rate at follow-up inferior to men operated on due to bothersome LUTS. We did not find this very surprising; we considered this to be a finding that could possibly be due to a permanent damage of the detrusor muscle. This, according to recent reports, should not preclude a TURP [146,147]. In recent years, evidence has been brought forward showing that detrusor underactivity points towards a less favourable outcome after TURP [148,149]. Perhaps the relatively high proportion of non-responders in the CISC group of patients was due to underdiagnosed chronic retention.

Although nine out of ten subjects responded to the surgical procedure employed, one tenth failed to respond and, in fact, most of these men were in retention prior to surgery. This, we believe, points towards that fewer of these patients may experience amelioration as compared to subjects operated on due to bothersome LUTS. TURP is in fact, in many hospitals, undertaken without previous pressure flow studies and, hence, it cannot be excluded that many of these men in fact had an underactivity of their detrusor function rather than having a true bladder outflow obstruction. This notion has previously been put on show by others [150]. Although BOO is probably

more likely than DUA in men affected by BPE, the relative prevalence is not clear epidemiologically [151].

A meta-analysis by Osman et al [152] suggested that detrusor underactivity is present in up to 50% of men subjected to pressure flow studies for LUTS, and, moreover, several authors have reported on that patients with an underactive detrusor have a lower chance of responding to a TURP [148, 153, 154, 155]. Nevertheless, it has been shown that more than half of the men with detrusor underactivity might respond to surgery [156].

Many of the patients in our cohort were catheter dependent prior to surgery and this finding tallies fairly well with figures presented by others [12, 157, 158].

In patient group with disturbing symptoms, the success rate was based on the de Wildt criteria. These men were, in turn, trichotomized into those who responded, those who did not respond, and those who responded excellently. It turned out that the men who responded to surgery were fairly evenly spread between reaching up to one, two or three of the de Wildt criteria, respectively. These data could help us in counselling the patient prior to surgery; a man suffering from micturition disturbances can be counselled that he has a 25% chance of a very good result, and a chance of a fair outcome of 70%, but also that he runs a small risk of about 5% that the surgical procedure will be completely unrewarding.

When it comes to non-responders after TURP for the men suffering from micturition disturbances, it appears that using established criteria for success can be questioned. If the surgical procedure should end up in a reasonable amelioration in all four domains of the de Wildt criteria without reaching up to the arbitrary cut-off level in any criterion, the patient might indeed, although regarded as a subject not responding, still find himself improved. And this is also true the other way around, a patient fulfilling only one criterion will, by definition, be a responder even if he does not experience any (or very little) amelioration at all.

Out of the nine subjects failing to respond to surgery for bothersome micturition disturbances, six had in the end a satisfactory voiding. Maybe, these men should not be regarded as non-responders but instead as examples of prolonged wound healing. Persisting symptoms after a TURP can perhaps be due to several causative factors, for example, remaining obstruction due to insufficient resection, neurogenic detrusor instability, or a urinary tract infection [20, 159, 160]. A minimum time to follow-up after one year for

randomised controlled trials is in fact recommended by the International Consultation of Benign Hyperplasia [161]. In light of this, an assessment after three months might perhaps be too early for bladder remodeling to take place [162].

Indeed, the paths for our patients not responding to primary surgical intervention were diverging. This is not only true for follow-up regimens but also for all the decisions made when it came to additional diagnostic measures and supplementary surgery. But why was this the case? Speculatively, these differences mirror that there were many urologists involved in all aspects of the care of the patients. Having said this, we certainly found that several patients, unresponsive to primary surgery, responded to redo surgery. Could it be that even more men could have been helped by an additional surgical procedure? Maybe, using pressure flow studies more eagerly in the non-responders would have identified more men with residual obstruction, men that maybe could have responded well to redo-surgery.

No doubt, some hundred years ago when TURP was new, complications were very common and mortality rates were high. The employment of better equipment and better surgical training, in association with improved anesthesiologic techniques, have turned TURP into what is now considered to be a safe procedure. Nevertheless, the Swedish Council on Health Technology Assessment also pointed out the need for research also in this respect, particularly from non-academic hospitals. Taking on this challenge, using the Clavien-Dindo scale, we could confirm that complications were minor to moderate and that the frequency of high-grade complications was diminutive. Grade IV and V complications were extremely rare. Re-interventions were not that very rare, however. It rather reached up to some 10%, tallying with what has previously been reported [14, 163]. Bleeding in association with TURP is positively correlated with a high prostate volume, many minutes (hours) of surgery, a lot of prostatic tissue to be removed, and the use of anticoagulation or antiplatelet medication [164]. The percentage of patients having blood transfusions was low in the present series, reflecting the modest volume of bleeding.

Some patients were unable to pass urine after TURP. Yet, we believe that the inability to void after a TWOC, following resection of prostate should perhaps not be seen as a complication per se, but rather judged to be an undesired postoperative course. For a man with an indwelling catheter it is quite common not being able to void straight after a resection of the prostate.

A man still dependent upon a catheter at follow-up may very well be suffering from detrusor underactivity [153,165].

In this patient cohort, only two episodes of TUR syndrome were noted. Perforating the capsule and venous sinuses early on during the operation may bring about the absorption of inert fluid and subsequent low levels of plasma sodium and water intoxication, this TUR syndrome having been reported to be in the order of 1% [166]. In our series, TURP was undertaken with the frequency of TUR syndrome of 0.6%.

Complications in the long-term have previously been demonstrated to arise at rates varying between 2.2–9.8% for urethral strictures, rates between 0.3–9.2% of contractures of the bladder neck, and an overall re-intervention rate of 3–14.5% [167]. Our study shows somewhat similar corresponding long-term complication rates. Tasci et al. [9], reported figures from a large cohort study, showing that urethral strictures and contractures of the bladder neck occurred in accordance with the figures presented in our study.

Using the Clavien-Dindo grading system for categorising complications after surgery emphasises a particular undesired event following surgery and highlights the strength of intervention necessary to manage that event. [143]. A modification of the Clavien-Dindo system, as reported by Mamoulakis and colleagues [144], characterises a simple and easily applicable tool that should aid urologists to categorise adverse events after TURP in a more detailed and objective manner. It can be used as a standardised platform of communication between urologists which allows for adequate evaluations to be made between studies. Nevertheless, some limitations exist as the Clavien-Dindo classification system in general is only applicable to postoperative and not to complications occurring during the actual procedure [145].

A possible limitation of our **Paper II** was that the TURP procedures were performed by a group of urologists with substantial variation in surgical experience, and including urological residents. However, this could also be interpreted as a strength of our study as the findings probably are generalizable and maybe also mirror what actually happens at most urological departments.

In the descriptive cohort (**Paper IV**) of 122 men who underwent planned TURP procedures during 2017-2019, at Skaraborgs Hospital, the median total cost per patient was 37343 SEK (€ 3361). Davis and colleagues evaluated men subjected to a TURP in five different European countries and found a substantial variation in mean total costs ranging from €2138 in the

UK and €5644 in Germany depending on the comorbidity status of the patient [168]. Bjerklund Johansen and his colleagues examined the DRG costs for TURP and also found considerable variation in total costs between €3665 and €4670, depending on the comorbidity status [169]. We have found similar results in our study. We found that the variation in total costs could, to some extent, be explained by patient age, prostate volume and preoperative urinary retention. However, our multivariable model of predicting total costs could merely explain 14% (R^2 adjusted = 0.140) of the cost variation.

On the other hand, the postoperative factors of catheter time, length of stay and occurrence of postoperative complications were all heavily associated with increased total cost. For every extra hour the average patient was catheterised postoperatively, the total cost increased by 370 SEK and for every extra day the patient occupied a bed at the ward the total cost increased by 8215 SEK. A single individual suffering from any type of postoperative complication had an average increased cost of 18300 SEK as compared to an uncomplicated procedure. To the best of our knowledge, this question has not been specifically addressed before.

6 CONCLUSIONS

Based on the findings in the first paper of this thesis (**I**), we can conclude that TURP is a rewarding surgical procedure in men suffering from bothersome urinary tract discomfort as well as men with the inability to void due to prostate enlargement. We, however, noted that patient age and comorbidity were somewhat determining factors for outcome. We therefore conclude that it is important to take these factors into consideration when counselling the patient prior to surgery. We, moreover, believe that there are considerable differences, as for outcome parameters, in men operated on with a TURP depending on the reason behind the decision to embark upon surgery; complete voiding but with severe LUTS or inability to void. These two groups should preferably be investigated separately, particularly when, in the future, comparing TURP against other and perhaps novel treatment techniques.

With regard to our findings in the second paper of this thesis (**II**), we conclude that TURP, undertaken in a setting as ours, seems associated with a low perioperative morbidity and, hence, that it should still be considered as the gold standard procedure and recommended to men suffering from problems related to BPE. In this context, we also conclude that the Clavien-Dindo classification is a simple, standardized and straightforward approach of grading and reporting post-operative complications related to the TURP procedure.

However, not all men subjected to TURP will respond favourably to surgery, as shown in our third paper (**III**). Nevertheless, we found that almost one in three men, at follow-up judged to be non-responders, will eventually have a satisfactory outcome with or without redo surgery. We, moreover, conclude that urodynamic studies are underused in a setting as ours.

When studying the money spent on a TURP procedure (**IV**) in the real-time world, we ended up with the conclusion that our data correspond fairly well with previous reports. We also noted that age, prostate volume, and preoperative urinary retention did not predict the risk for an increased total cost for a TURP. Rather, we can firmly conclude that the most important and striking finding was the very strong association between complications and total costs.

7 FUTURE PERSPECTIVES

Adherence to guidelines and cost-effectiveness

Studies on the natural history of LUTS attributed to BPE have clearly shown an improvement and even an amelioration of symptoms in about 30% of patients. Thus, many patients with bothersome symptoms can and should be evaluated, diagnosed and treated in primary care prior to considering referral to an outpatient urology clinic. Several guidelines have been created in order to aid and standardize the shared care of this large patient group. Adherence to such guidelines has unfortunately been poor in Sweden.

There is evidence showing that there is a considerable discrepancy in practice in supporting the care of men with BPE, not only by physicians in general but also, worryingly within the urological community [170, 171]. In some health regions in Sweden, the chance of a man receiving a surgical intervention against BPE is five times higher than in other regions. A similar pattern can be demonstrated regarding the prescribing of pharmacotherapy to relieve LUTS related to BPE. From an ethical standpoint, this cannot be an acceptable way of providing equal care for this group of men.

The reasons behind the discrepancy in care, and the steady decline in the amount of TURP procedures performed during the last three decades, are presumptively multifactorial. The advent of pharmacotherapy led to a paradigm shift in the treatment of LUTS/BPH. This shift may have been taken too far as there are questions being raised as to whether we are deterring effective surgical intervention due to over-prescription of medical therapy. This might save time in the short term, but are we really using available evidence to provide the most cost-effective care in the long run?

A cost-effectiveness study comparing combination pharmacological therapy with TURP would be interesting to investigate over a three-year period. Speculatively, pharmacological therapy could have the potential to postpone the need for a TURP but with the possible risk of inflicting more serious complications and as such submitting men with a more advanced BPE for surgery. Previous studies have indicated conflicting results as to whether TURP is the most cost-effective regime, in men with moderate to severe LUTS, as compared to pharmacological treatment, as initial treatment [168, 172, 173, 174].

The routine use of urodynamics prior to TURP

In most countries, including Sweden, there is a considerable variation in the practice of urodynamic investigations, reflecting the continuing debate as to whether urodynamics should be used in the routine work-up prior to TURP [175]. Some urologists advocate its use with the argument that it determines which man has obstruction and should, as such, benefit from surgery and could avoid intervention in a man not having obstruction and not exposing these men to surgery with the risk of serious adverse events. Others support a more restricted use of urodynamics due to the potential risks of complications, perceived unpleasant experience, and the associated costs of the procedure [176, 177]. So far, systematic reviews examining the outcomes of urodynamics have been inconclusive [178, 179].

A recent study by Young et al, examining the shifting practice in TURP, could show that the average age and the comorbidity status has gradually increased over the years. The most common reason for a TURP has changed from bothersome LUTS to urinary retention. There has been a marked increase in men with dysfunction of the bladder who either have persisting LUTS or eventually require long-term CISC after a TURP. This is a strong argument for the routine use of urodynamics including pressure flow studies, especially in patients who have suffered from urinary retention. I am eager to learn the results of the ongoing UPSTREAM trial designed to answer whether a man would credibly benefit from relief of BPO and whether there are any risk factors for developing complications during surgery [180].

Quality Assurance

Mirroring the national cancer care programs for urological cancer, a contemporary national care program for BPE needs to be devised in the near future. This should enable a more standardised care for this group of men.

Sweden has several National Quality Registries containing individual data on the diagnosis, medical or surgical intervention, and outcomes after treatment. A national register of all surgical interventions carried out on BPE should be established which should provide a substantial research base and through quality assurance enable improved outcomes and equal care for our patients.

There is a need for qualitative studies using formal validated methods, interviewing men on their thoughts, feelings and expectations encountered in

conjunction with a TURP procedure. Previous studies have explored the extent to which spouses and health providers outside the hospital are affected during the initial postoperative period. In addition to well-known postoperative symptoms of urgency, dysuria, intermittent incontinence and bleeding, interviews have also revealed a significant amount of sleep disturbances, anxiety and negative impacts on social life. These men and their family members need support.

From our own patient cohorts, we have gathered valuable information on men's perception regarding voiding three months after TURP. Comments include positive aspects, for example:

"I am very satisfied with the result of the operation"

"My voiding is much improved"

"I should have done this years ago"

"I feel much more alert during the day as I now am able to sleep through the whole night"

"I feel young again, the clock has been turned back almost 30 years..."

But also, negative aspects like:

"I was not informed about the risks of erectile dysfunction"

"I still suffer from urgency"

"I still need to wake up and go to the toilet three times every night"

Urological training

The operative exposure of urological trainees in the UK was assessed over a six year period [181]. There was a decline in the number of TURPs performed by trainees during this time frame.

In the same time frame, colleagues in the United States, noticed similar trends in decline in numbers of procedures performed but also that the amount of surgical complications, as measured by the requirement for succeeding re-interventions, had risen suggesting a learning curve effect [182]. Most procedures require a certain number of cases in order for the urological surgeon to become adept. This is the concept of the learning curve and has previously been studied for many procedures including radical retropubic prostatectomy where it takes approximately 250 cases to reach the plateau of the learning curve with respect to oncological outcomes [183]. The learning curve of endoscopic procedures, and TURP in particular, has not been subjected to rigorous study. It has previously been suggested that it might take up to 50 cases before becoming comfortable with holmium laser enucleation, a complex procedure not too dissimilar from TURP [184, 185].

Competence-based training, rather than the traditional time-based approach, should be strived for. It rests with both the trainer and the trainee to ensure that competence is reached, and excellence is sought. Live surgery demonstrations, dry and wet lab laboratory training and enhanced simulation training will all help in this aspect.

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