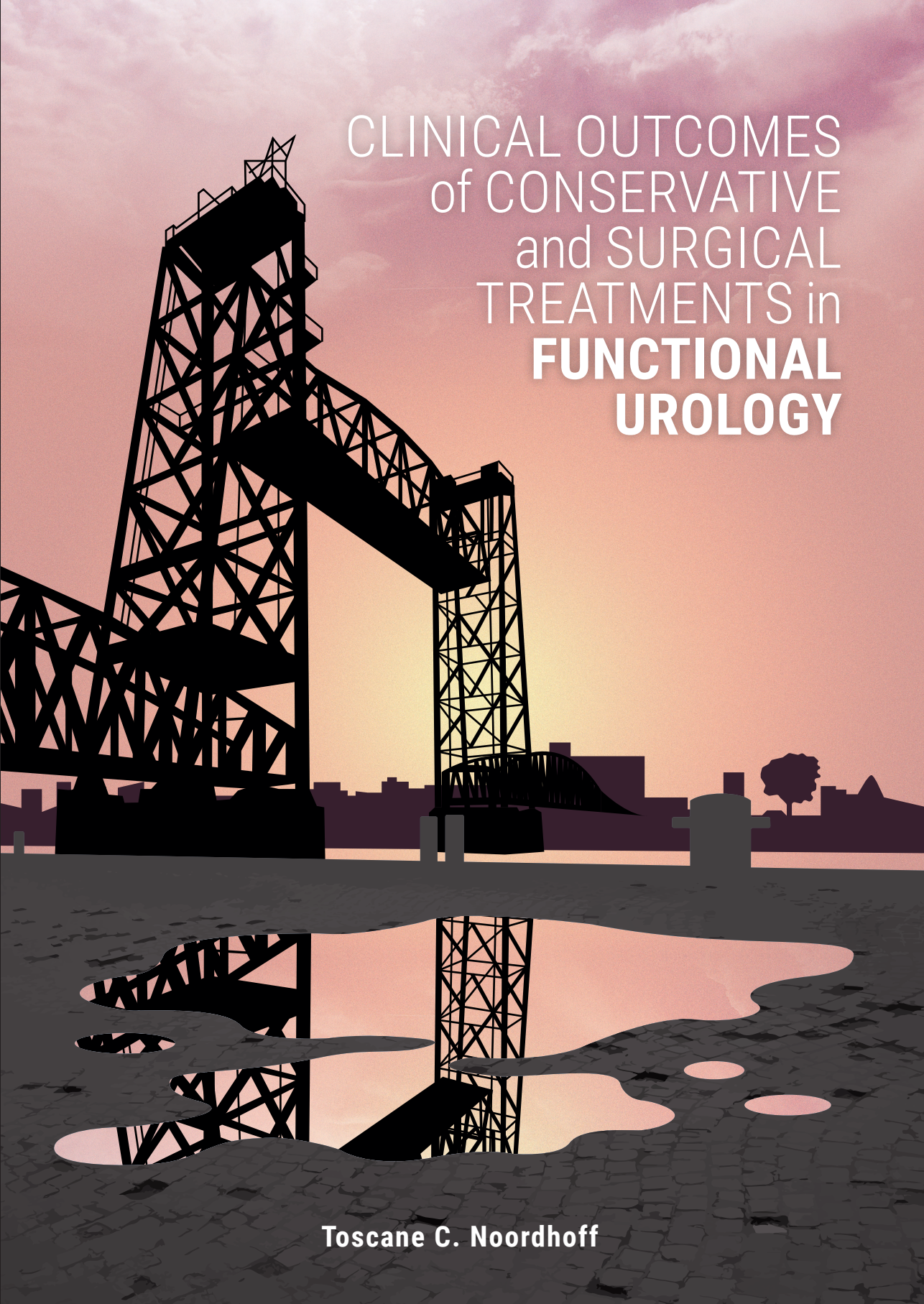
CLINICAL OUTCOMES
of CONSERVATIVE
and SURGICAL
TREATMENTS in
FUNCTIONAL
UROLOGY
Toscane C. Noordhoff

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CLINICAL OUTCOMES of CONSERVATIVE and SURGICAL TREATMENTS in **FUNCTIONAL UROLOGY**

COLOPHON

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CLINICAL OUTCOMES OF CONSERVATIVE AND SURGICAL TREATMENTS IN FUNCTIONAL UROLOGY

Klinische uitkomsten van conservatieve en chirurgische behandelingen
binnen de functionele urologie

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CONTENTS

CHAPTER 1

General introduction

FUNCTIONAL UROLOGY

The field of functional urology deals with functional disorders of the lower urinary tract (LUT), which consists of the urinary bladder and its sphincters, and the pelvic floor. The main function of the LUT is storage and voiding of urine.[1] The activity of the urinary bladder and bladder outlet is determined by a complex set of peripheral autonomic and somatic nerves controlled through intact neural pathways in the spinal cord and brain.[2] Normally, during the urine storage phase the external urethral sphincter is contracted and the detrusor is relaxed. At the initiation of the voiding phase, voluntarily initiated continuous detrusor contractions occur after the external urethral sphincter opens to allow the bladder to be emptied at a normal pressure.[1,3]

Regarding the pelvic floor, function is important in both urinary and fecal continence, sexual function and support to the pelvic organs. The pelvic floor consists of muscles, bone attachments, and fascial components.[4] Fecal continence is achieved by a complex interactive coherence between muscle groups of the pelvic floor and sphincter complex, rectal compliance, consistency of stool, and cognitive function.[5] During normal defecation, a contraction of the rectum and perineal muscles simultaneously with a relaxation of the anal sphincter results in stool evacuation.[6] For normal sexual function desire, arousal, and orgasm are important.[4,7] In female sexual function, the pelvic floor has a critical role in addition to maintain bladder and bowel continence, and pelvic support. The exact role in male is unclear, although it appears to have some influence on sexual function.[7]

Clinical evaluation of LUT and/or pelvic floor dysfunction is based on the following four domains: urinary, anorectal, sexual dysfunction, and pelvic organ prolapse. Patients may experience symptoms in more than one domain.[3,8,9] Selected common symptoms of each domain are described below:

Urinary symptoms - LUT symptoms can be related to the storage phase, voiding phase or post voiding phase. Examples of symptoms during storage phase are: frequency, nocturia, urgency, and involuntary leakage of urine. Urinary incontinence can be divided into: stress-, urge-, and mixed urinary incontinence. Involuntary leakage from the urethra synchronous with effort, or coughing, or sneezing is defined as stress urinary incontinence. Urge urinary incontinence is involuntary leakage from urethra accompanied with the sensation of a sudden desire to void difficult to defer. Mixed urinary incontinence is associated with both stress and urge urinary incontinence.

During the voiding phase, symptoms of hesitancy, weak or intermittent stream, or straining can occur. Feeling of incomplete emptying and post micturition dribble are examples of symptoms experienced immediately after micturition.[1,3]

Anorectal symptoms - Disorders of anorectal function include defecation disorders, fecal incontinence, and proctalgia syndromes.[6,10] A defecation disorder is characterized by difficulty in evacuating stool from the rectum resulting in chronic or recurring symptoms. The cause of a defecation disorder can be functional or structural or coexisting anorectal disturbance.[10] Fecal incontinence is associated with symptoms of involuntary loss of flatus, liquid, or solid stool.[5,10] The etiologies can have congenital causes (spinal cord defects and anorectal malformations), acquired causes (obstetrical injury or anorectal surgery), and nonstructural causes (e.g. infectious colitis, side effects of medication).[5] Patients with proctalgia syndromes experience rectal pain.[10]

Sexual dysfunction - The cause of sexual dysfunction could be any experienced problem or symptom influencing normal sexual function. In women, symptoms of sexual dysfunction may occur together with other pelvic floor symptoms such as urinary incontinence, fecal incontinence, or pelvic organ prolapse. Low sexual desire and arousal, infrequent orgasm, and dyspareunia are associated with pelvic floor symptoms.[4] The two most prevalent male sexual dysfunctions are erectile dysfunction and premature ejaculation.[11]

Pelvic organ prolapse - Laxity or weakness of the pelvic floor muscles and ligaments can result in a prolapse with or without symptoms. Possible symptoms include the sensation of prolapse, low back pain, the need to digitally replace the prolapse in order to defecate or void, or problems with sexual intercourse. In women, an uro-genital prolapse can occur when one or more structures (the anterior vaginal wall, the posterior vagina wall, and the apex of the vagina) have descended.[1,3] Rectal prolapse may present with symptoms such as anal protrusion, rectal pain, fecal incontinence or constipation.[6]

PATIENT POPULATIONS

Gender, age, and the presence of a neurological condition may influence the relevance, severity and bother of symptoms, as well as the management of LUT and pelvic floor dysfunctions. A health care professional can gain much information from the way in which a patient enters the consultation room. For example, the walking pattern or the need of any assistance (manual/electric wheelchair, walking device) may reveal a neurogenic role in the origin of the complaints.

Within the field of functional urology, it is important to distinguish the neuro-urological patients from the non-neuro-urological patients. Neurological conditions can cause urological symptoms due to any disturbance of the neural pathways that coordinate the LUT. It is mainly the extent and location of the neurological lesion that determine the severity and nature of the urological symptoms. Both adults and pediatric neuro-urological patients, are at risk for functional disturbance of the urinary tract with possible irreversible deterioration of the lower and upper urinary tract on the long term.[12] The origin of a neurogenic bladder dysfunction can be congenital, like spina bifida, or acquired, like traumatic spinal cord injury.

In children without a neurological condition, urinary continence (normal storage and emptying of the bladder) is expected around the age of four. Children with LUT conditions in the absence of congenital anatomical or neurologic abnormalities may present with urinary symptoms due to malfunction of the storage phase, the voiding phase, or both.[13] The International Children's Continence Society (ICCS) grouped all these functional bladder problems under the term day-time LUT conditions. Often comorbidities are encountered concomitantly with LUT conditions, such as constipation, fecal incontinence, urinary tract infections, nocturnal enuresis and psychiatric disorders.[13-15]

MANAGEMENT

Symptoms of LUT and pelvic floor disorders can have a negative impact on the quality of life of men, women and children. In the evaluation of symptoms of LUT and pelvic floor dysfunction, assessment of patient history and physical examination are essential. If relevant, additional investigations can be done, such as bladder and bowel diaries, urinalysis, urodynamics, measurement of post void residual urine, ultrasound, and lab test of renal function.[3,4,10-13] Conservative treatment could be the first step in the treatment of LUT and pelvic floor disorders, including lifestyle modifications, urotherapy, pelvic floor therapy or psychological therapy. Besides non-pharmacological therapy, a variety of pharmacological treatments can be given in combination with other conservative treatment. If conservative treatment is unsuccessful or suspected to be unsuccessful, a surgical intervention could be considered. Various surgical treatments are available ranging from minimally invasive to complex reconstructions. For example, for the male stress urinary incontinence various surgical treatment options are available like injection of urethral bulking agents, adjustable continence balloons, male sling, or artificial urinary sphincter.[16] In general, the aim of each treatment modality is to reduce the symptoms of LUT and pelvic floor disorders using a stepwise approach in consensus with the patient's perception of the bothersomeness of the symptoms.

LUT and pelvic floor disorders may present in neuro-urological patients in various ways. The main challenging urological goals in the management of neuro-urological patients, both adults and children, are to preserve the lower and upper urinary tract function, to maintain or achieve urinary continence, and to improve the quality of life.[12,17] In case of neurogenic urinary incontinence, conservative treatments such as clean intermittent catheterization and anticholinergic medications could be considered. If conservative therapy fails, a surgical option to increase the bladder outlet resistance could be discussed, such as bladder neck sling, bladder neck reconstruction, artificial, and injection of bulking agents.[18-22] These bladder outlet procedures can be combined with bladder augmentation to improve bladder capacity and/or continent catheterizable urinary channel for catheterization.[18-20,22] In general, recognizing the neuro-urological origin and problem is important in determining personalized treatment goals. Guidelines for the management of neuro-urological adults and children are available.[12,17,19]

OUTCOME MEASURES: TRADITIONAL AND PATIENT REPORTED

The International Continence Society (ICS) defined five domains to describe outcome in patients with LUT dysfunction: the patient's observations, quantification of symptoms, the clinician's observations (anatomic and functional), quality of life, and socioeconomic measures. To evaluate the effect of an intervention an assessment before and after the intervention is mandatory. The chosen outcome measure determines the effect of an intervention, which may vary between or within the domains. Therefore, a multidimensional approach is preferred, in particular because of the possible patient-physician discrepancy.[23,24] Traditional outcome measures, such as bladder and bowel diaries, pad tests, measurement of post void residual urine volume, assess the presence of symptoms, but do not assess the impact on quality of life or symptom bother from the patient's perceptive. When evaluating treatments of LUT and pelvic floor disorders, traditional outcome measures may give insight in quantitative changes of symptom presence. The outcomes may be converted into a symptom reduction rate when treatment is evaluated. For example, treatment outcome is defined by the ICCS as no response (<50% reduction of LUT symptoms), partial response (50% to 99% reduction of LUT symptoms), and complete response (100% reduction of LUT symptoms).[13] Conversely, LUT symptoms and impact on quality of life may not be equally assessed by patient and physician.[25,26] A physician's perception of symptom bother and idea of cure can be in discrepant from the patient's perception. This is why it is important to collect patient reported outcomes besides traditional outcomes.

Nowadays, various patient reported outcome measures (PROMs), usually in the form of validated standardized self-administered questionnaires, are available to capture patients' perspectives of health, disease, and effect of intervention. Subjective perceptions can be objectivized as quantifiable measure. The challenge is to choose the appropriate condition-specific or generic questionnaire available in the preferred language. Besides, most questionnaires are not comparable with each other and their quality varies. In order to achieve more insight into the quality of a questionnaire, measurement properties such as validity and reliability can be determined.[27]

Several PROMs are available in Dutch and validated to evaluate the domains of dysfunction of the LUT and pelvic floor in non-neurogenic patients. The use of a validated and appropriate questionnaire is recommended by the guideline on Urinary Incontinence of the European Urology Association when standardized assessment is required.[28] The Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) are validated questionnaires in Dutch to assess symptom distress of urinary incontinence and its impact on daily life in both men and women.[29] The fecal incontinence the Fecal Incontinence Quality of Life (FIQL) and the Fecal Incontinence Severity Index (FISI) can be used to evaluate bowel complaints and fecal incontinence.[30] The pelvic organ prolapse domain can be evaluated with the Pelvic Floor Distress Inventory (PFDI-20) and the Pelvic Floor Impact Questionnaire (PFIQ-7).[31] To assess sexual function in men, the International Index of Erectile Function short form (IIEF-5)[32] is available and for women the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire(PISQ-12)[33]. The Dutch Vancouver Symptom Score for Dysfunctional Elimination Syndrome VSSDES is a validated questionnaire to assess symptoms of bladder and bowel dysfunction in children.[34] To assess the impact of urinary incontinence on children's quality of life the Dutch Pediatric urinary incontinence Quality of life (PinQ) questionnaires can be used.[35] According to the International Children's Continence Society, both questionnaires are appropriate and useful tools.[13]

The guideline on Neuro-urology of the European Urology Association states that assessment of quality of life is essential in the overall management of neuro-urological patients.[12] In neuro-urological patients it is important to use condition-specific PROMs specially designed for this population. Compared to the non-neurogenic population, symptom bother may differ and additional symptoms may be present due to the neurological condition. The Dutch SF-Qualiveen is a validated short questionnaire to measure the urinary-specific quality of life in patients with a neurological condition.[36,37] Validated Dutch questionnaires to evaluate sexual function and anorectal symptoms in neuro-urological patients are still missing.

The routine use of PROMs in oncology have resulted in better communication between patient and physician, greater patient satisfaction, detection of unrecognized problems, and improvement in monitoring of treatment response.[38] The combination of traditional and patient reported outcomes could possibly give more insights in the evaluation of symptoms within functional urology.

FOCUS OF OUR RESEARCH GROUP

Our research group has been devoted to research in the field of functional disorders of the urogenital tract in men, women and children. The focus of our clinical research line is testing the psychometric measurement properties of PROMs and evaluating traditional and patient reported outcomes of treatments within this field. The main goal is to optimize care in individuals by building bridges between patients, physician, and researcher. This research line is continued in this thesis.

AIMS OF THIS THESIS

This thesis aims to evaluate effectiveness of conservative and surgical treatment in functional urology, reflected by traditional and patient reported outcome measures. A distinction is made between neurogenic and non-neurogenic patients. The effectiveness of conservative therapy in non-neurogenic children, two surgical interventions in children with a neurogenic condition and one surgical intervention in two different groups of non-neurogenic men are evaluated. To establish an optimal practice, the outcomes of different surgical interventions in a neurogenic population are assessed. Additionally, focus is placed on providing validated Dutch versions of PROMs that evaluate sexual function in neurogenic adults and urinary and anorectal symptoms in non-neurogenic children.

OUTLINE OF THIS THESIS

Part I. Evidence based outcome in functional urology

In the first part of this thesis, **chapter 2**, the focus is to identify an effective treatment option according to evidence based medicine. Different surgical therapies for the treatment of anatomic bladder outlet obstruction in males with neurogenic bladder dysfunction are systematically reviewed.

Part II. Outcome of surgical treatment in functional urology

In this part the outcomes of different surgical treatments to manage urinary incontinence are described. The long-term results of bladder outlet procedures such as bladder neck sling and bladder neck reconstruction in children with neurogenic urinary incontinence are evaluated in **chapter 3**. **Chapters 4 and 5** focus on outcomes, complications and re-interventions of minimally invasive continence therapy named ProACT™ in non-neurogenic men with stress-urinary incontinence after radical prostatectomy and transurethral resection of the prostate. The patients' overall response to the intervention is assessed with the Patient Global Impression of Improvement scale.

Part III. Patient reported outcome measures in functional urology

Different internationally accepted PROMs were translated into Dutch and their measurement properties were evaluated. The Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-15) evaluates symptoms of sexual dysfunction in multiple sclerosis patients. In **chapter 6** the translation and validation process of the Dutch MSISQ-15 in patients with neurological disease such as multiple sclerosis and spinal cord injury is described. **Chapter 7** evaluates the responsiveness of the Dutch Vancouver Symptom Score for Dysfunctional Elimination Syndrome (VSSDES) and the Dutch Pediatric urinary incontinence Quality of life score (PinQ) used in children with dysfunctional voiding. The VSSDES evaluates symptoms of bladder and bowel dysfunction. The effect of bladder dysfunction on the quality of life is measured with the PinQ. Besides, **chapter 7** describes the outcome of extended urotherapy for children with dysfunctional voiding.

Part IV. General discussion and summary

In **chapter 8** the added value of a therapy's effectiveness reflected by traditional and patient reported outcome measures is discussed in view of the results of this thesis and present literature. The implications for clinical practice and research, challenges in future research and future perspective are discussed.

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PART I

Evidence based outcome in functional urology

CHAPTER 2

Surgical management of anatomic bladder outlet obstruction in males with neurogenic bladder dysfunction: a systematic review

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ABSTRACT

Context: Surgical treatment of anatomic bladder outlet obstruction (BOO) may be indicated in males with neurogenic bladder dysfunction. A bothersome complication after surgery is urinary incontinence.

Objective: To identify the optimal practice in the surgical treatment of anatomic BOO in males with neurogenic bladder dysfunction, due to multiple sclerosis, Parkinson disease, spinal cord injury (SCI), spina bifida, or cerebrovascular accident (CVA).

Evidence acquisition: A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Medline, Embase, Cochrane controlled trial databases, Web of Science, and Google Scholar were searched for publications until January 2017.

Evidence synthesis: A total of 930 abstracts were screened. Eight studies were included. The types of anatomic BOO discussed were benign prostate obstruction, urethral stricture, and bladder neck sclerosis. The identified surgical treatments were transurethral resection of the prostate (TURP) in patients with Parkinson, CVA or SCI, endoscopic treatment of urethral stricture by laser ablation or urethrotomy (mainly in SCI patients), and bladder neck resection (BNR) in SCI patients. The outcome of TURP may be highly variable, and includes persistent or de novo urinary incontinence, regained normal micturition control, and urinary continence. Good results were seen in BNR and endoscopic urethrotomy studies. Laser ablation and cold knife urethrotomy resulted in restarting intermittent catheterization or adequate voiding. Overall, a high risk of bias was found.

Conclusions: This systematic review provides an overview of the current literature on the outcome of several surgical approaches of different types of anatomic BOO in males with neurogenic bladder dysfunction. Identifying the optimal practice was impossible due to limited availability of high-quality studies.

Patient summary: The outcome of several surgical approaches in males with neurogenic bladder dysfunction with benign prostate obstruction, urethral stricture or bladder neck sclerosis is overviewed. The optimal practice could not be identified.

1. INTRODUCTION

Symptoms of lower urinary tract (LUT) dysfunction in patients with neurological disease have an effect on the quality of life.[1] The type of the neurological disease and the location of the lesion determine the pattern of the neurogenic bladder dysfunction, which can be shown in various urological symptoms.[1,2] Symptoms in the absence of infection or obvious pathology other than possible causes of outlet obstruction are suggestive for bladder outlet obstruction (BOO).[3] Detrusor-sphincter dyssynergia is the most common form of BOO in people with a neurogenic bladder dysfunction.[4] However, BOO can also have an anatomic cause, such as benign prostatic hyperplasia (BPH) or urethral stricture. Surgical management of anatomic BOO may result in urinary incontinence (UI). Owing to the effects of neurological pathology on the LUT function, the surgical outcome in the treatment of anatomic BOO is expected to differ from that in the non-neurogenic population.

A feared complication in patients treated with intermittent catheterization (IC) is a urethral stricture due to repeated urethral trauma. IC is the gold standard for the management of neurogenic LUT dysfunction.[2,5] Benign prostatic obstruction due to BPH is a relatively common disease in older men. Fifty percent of the male population between 51 and 60 yr of age has LUT symptoms (LUTS) due to BPH.[6] Since male patients with a neurogenic bladder dysfunction can have an age of >50 yr and be at a risk of urethral strictures, treatment for BPH or urethral stricture could be necessary. Surgical interventions for anatomical BOO are transurethral resection of the prostate (TURP), open prostatectomy, bladder neck resection (BNR), endoscopic urethrotomy, and urethroplasty.

This systematic review focused on the surgical management of an anatomic BOO in males with a neurogenic bladder dysfunction due to multiple sclerosis (MS), Parkinson disease, spinal cord injury (SCI), spina bifida, or stroke/cerebrovascular accident (CVA) in order to identify optimal practice.

2. EVIDENCE ACQUISITION

2.1 Study registration

This systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions[7] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[8]. The study protocol was registered on PROSPERO (CRD42017055229; https://www.crd.york.ac.uk/PROSPERO).

2.2 Literature search

The citation sources Web of Science and Google Scholar and the Medline, Embase, and Cochrane controlled trial databases were searched for all relevant publications until January 2017. No date restrictions were applied. Duplicates were removed. The reference list of the relevant reviews was searched for relevant articles. The complete search string is shown in the Supplementary material.

2.3 Eligibility criteria

All publications on surgical treatment of anatomic BOO caused by BPH, urethral stricture, or bladder neck sclerosis in male patients aged >18 yr and neurogenic bladder dysfunction due to MS, Parkinson disease, SCI, spina bifida, or stroke/CVA were eligible for full-text retrieval. The different types of interventions were TURP, open prostatectomy, endoscopic urethrotomy, urethroplasty, BNR, or any other surgical treatment for anatomic BOO. This review did not address surgical treatment of functional BOO due to neurogenic bladder dysfunction. Cancer was an exclusion criterion. Case reports with <10 adult neuro-urological (NU) patients, non-English text articles, conference abstracts, and reviews were excluded. The study population of all studies had to treat >90% adult NU patients, or the results for adult NU patients were separately reported.

2.4 Selection of studies

Two reviewers (T.N. and J.G.) independently screened the titles and abstracts in Endnote (EndNote X7; Thomson Reuters, Philadelphia, PA, USA). The full text of all potentially eligible publications was independently screened by the same reviewers using a standardized screening form. A third reviewer (B.B.) resolved any disagreements between the two reviewers.

2.5 Data extraction

The predefined data were independently extracted from the included full-text publications by two reviewers (J.G. and T.N.) using a standardized form. Any disagreements were resolved by the third reviewer (B.B.). General characteristics of the studies and study populations included the type of study, country, number of patients, age, neurological disease, type of anatomic BOO, type of intervention, and type of outcome measures.

2.6 Outcome measures

The measures of the outcome of the intervention were divided in primary and secondary outcomes.

Primary outcomes:

1. Degree of UI (pad use)
2. Results of invasive and non-invasive urodynamic measurements

Secondary outcomes:

1. Quality of life
2. Adverse effects after treatment
3. Surgical outcome measures
4. Renal function
5. Socioeconomic measures
6. Other outcomes: non-prespecified outcome important when performing the review

2.7 Subgroup analyses

The predefined subgroups were type of anatomic BOO, type of intervention, and underlying NU pathology.

2.8 Risk of bias assessment

The Cochrane Risk of bias Assessment Tool[7] together with an assessment of the main confounders following recommendations of the Cochrane handbook for nonrandomized comparative studies[9] were used to perform a risk of bias analysis for included nonrandomized comparative studies. We developed a list of main confounders. The identified confounders were age, underlying NU pathology, previous treatments for anatomic BOO, and previous surgeries of the LUT. During data extraction, the identified confounders were analyzed in the studies. Confounding bias was classified as "high" if the confounder was unadjusted during analysis, imbalanced between the groups, or not considered or described. To determine the risk of bias for noncomparative studies, the availability of a priori protocol, selective outcome reporting (reporting bias), and incomplete data outcome (attrition bias) was assessed. Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) was used to compute the risk of bias figure.

3. EVIDENCE SYNTHESIS

3.1 Search results

The PRISMA flow diagram in Figure 1 shows the results of literature search and study selection. The initial literature search resulted in 930 abstracts. After reviewing 84 full-text articles, eight studies were included.[10-17]

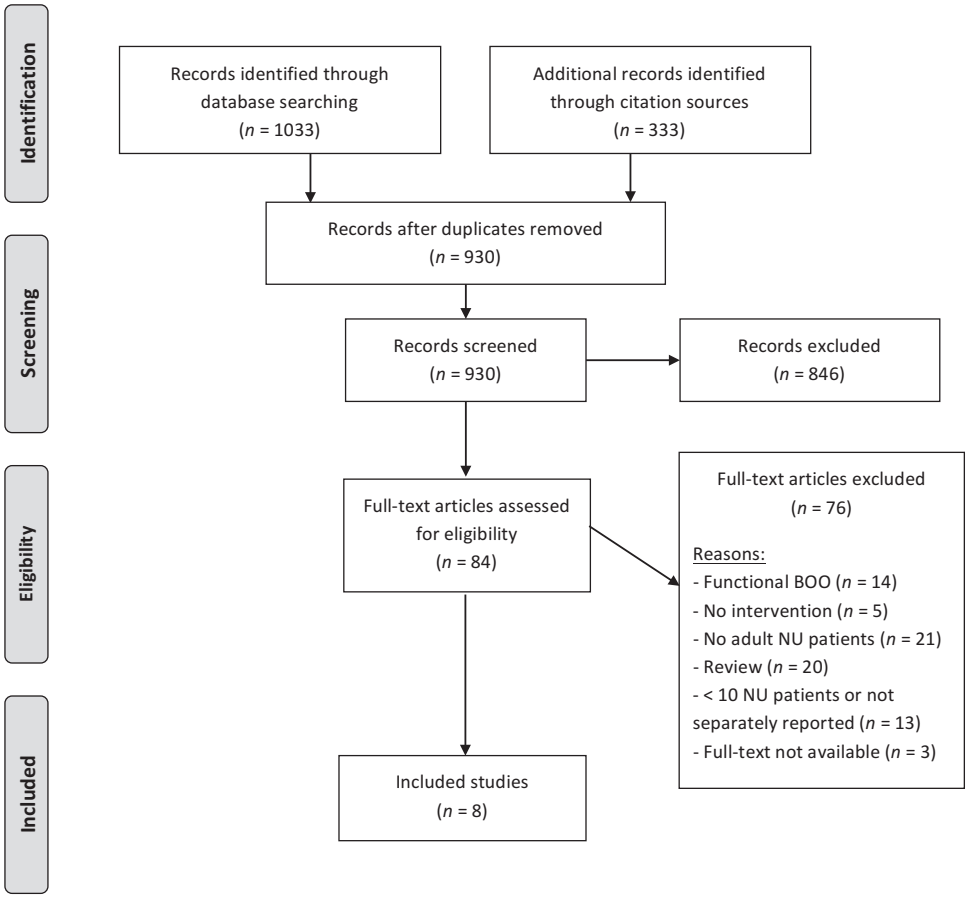

FIGURE 1. The literature search and study selection. BOO = bladder outlet obstruction; NU = neuro-urological; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

3.2 Characteristics of included studies

3.2.1 Design of studies

Table 1 shows the descriptives of the included studies. They were all retrospective and published between 1972 and 2017. The design of two studies was comparative, and the other six studies were single-arm studies. A total of 333 NU patients with an anatomic BOO were included in the studies, and 251 of them underwent a surgical treatment for anatomic BOO. All study participants were included consecutively.

3.2.2 Underlying neurological disease

Of the 333 included patients, the neurogenic bladder dysfunction was due to SCI in 201 men[11,12,14,16], Parkinson disease in 73 men[10,17], CVA in 53 men[13,15], spina bifida in four men[12], and MS in two men[12].

3.3 Identified treatment

The interventions reported in the included studies were TURP, endoscopic urethrotomy, BNR, urethroplasty, and meatotomy. One single treatment was applied in six studies. More than one treatment modality was applied in two studies. However, in these studies urethroplasty and meatotomy were performed in <10 cases, and the results will therefore not be discussed here.[11,16] Most of the studies reported the results of a surgical treatment in one hospital. One study reported the results of eight institutions.[13] In the studies of Perkash[14] and Roth et al[10], one surgeon performed the interventions. The number of surgeons in the other studies was unclear.

3.3.1 Transurethral resection of the prostate

In five studies, results of TURP in men with BPH were described.

Roth et al[10] reported the outcome in 23 patients with Parkinson disease. All patients had refractory LUTS despite alpha blockers for ≥2 mo. The median age was 73 yr, and the median time since Parkinson disease was diagnosed 3 yr at the moment of TURP.

Han et al[13] evaluated which factors were associated with continued use of LUTS/BPH medication after TURP in 372 patients, including 31 with CVA.

Elsaesser and Stoephasius[16] described 46 SCI patients with anatomic BOO. This was due to BPH in 21 patients, who underwent a TURP. The time between the SCI and the TURP varied from 4 mo to 15 yr.

TABLE 1. Characteristics of the included studies.

Study	Study design	Recruitment period	NU patients / study population BOO	Type of NU patients	Type of anatomic BOO	Type of intervention	Age (yr)	Median time since NLUTD (yr)	Urological history	Urological drug history	Preoperative incontinence	Follow-up time
Roth et al (2009)	Retrospective single arm	1997-2007	23/23 (100%)	100% Parkinson disease	BPH	TURP	Median 73 (IQR 68–81)	Median 3 (IQR 1-5)	SPC in 11/23 TUC in 9/23 -Previous surgery NR	Alpha blockers for ≥ 2 mo	10/23 (43%) Urge incontinence 17/23 (74%) Detrusor overactivity	Median 3 (IQR 2-6) yr
Han et al (2014)	Retrospective comparative	2009-2011	31/372 (8%)	8% CVA 92% Non-NU patients	BPH	TURP	NR	NR	NR (entire population 6/372 previous BPH operation)	NR (entire population 295/372 BPH/LUTS medication)	NR	≥ 3 mo in all
Moisey and Rees (1978)	Retrospective single arm	1972-1976	22/22 (100%)	100% CVA (including 2 with CVA and Parkinson disease)	BPH	TURP	Range 58-93	< 2 yr in 14/22 2-11 yr in 8/22	13/22 Acute retention 3/22 Chronic retention 3/22 Symptoms of BOO -Previous surgery NR	NR	3/22 (14%) Urinary incontinence	NR
Statskin et al (1988)	Retrospective comparative	1977-1984	50/50 (100%)	100% Parkinson disease	36/50 BPH	36/50 TURP	NR (entire population mean 67, range 50-82)	NR (entire population median 9.7, range 1-28)	NR	NR	6/36 (17%) Urinary incontinence (4 urge and 2 overflow)	Mean 9.2 (range 1-28) mo
Perkash (1997)	Retrospective single arm	NR	42/42 (100%)	SCI 79% Complete 21% Incomplete	Urethral stricture: 30 bulbar 4 bladder neck & bulbar 5 anterior pendulous 3 prostatic	Transurethral contact laser ablation	Mean 48 (range 26-69)	NR	24/42 Electrocautery incisions extending into the bulbar urethra	NR	NR	Mean 28.2 (range 12 to 46) mo

TABLE 1. Continued.

Study	Study design	Recruitment period	NU patients / study population BOO	Type of NU patients	Type of anatomic BOO	Type of intervention	Age (yr)	Median time since NLUTD (yr)	Urological history	Urological drug history	Preoperative incontinence	Follow-up time
Cornejo-Dávila et al (2017)	Retrospective single arm	2001-2016	14/14 (100%)	100% SCI	Urethral stricture: 12 bulbar 1 penile 1 meatus	12 Endoscopic urethrotomy of bulbar stricture 1 meatotomy 1 no surgery	NR	NR	IC in 14/14 -Previous surgery NR	NR	NR	Mean 1 yr
Krebs et al (2015)	Retrospective single arm	2008-2012	105/105 (100%)	94% SCI 4% Spina bifida 2% MS	Urethral stricture: 10 bulbar 20 penile 8 multiple	38 Endoscopic urethrotomy	NR (entire population median 41, range 19-74)	NR (entire population median 5.0, range 0.1-48.9)	IC in 105/105 -Previous surgery NR	NR	NR	Median 14 (range 2-24) yr (entire population 15 (range 2-54) yr)
Elsaessand Stoephasius (1972)	Retrospective single arm	1969-1971	46/46 (100%)	100% Traumatic SCI	21 BPH, 7 meatus stenosis, 4 urethra stricture, 14 bladder neck sclerosis	21 TURP 7 Meatotomy 4 Urethroplasty 14 Bladder neck resection	NR	BPH: 4-6 months (*n*=6), 7-12 mo (*n*=9), 1-15 yr (*n* =6). Bladder neck sclerosis 4-6 mo (*n*=2), 7-12 mon (*n*=7), 1-13 yr (*n*=5)	NR	NR	NR	NR

BOO = bladder outlet obstruction; BPH = benign prostate hyperplasia; CVA = cerebrovascular accident; IC = intermittent catheterization; IQR = interquartile range; LUTS = lower urinary tract symptoms; MS = multiple sclerosis; NLUTD = neurogenic lower urinary tract dysfunction; NR = not reported; NU = neuro-urological; SCI = spinal cord injury; SPC = suprapubic catheter; TUC = transurethral catheter; TURP = transurethral resection of the prostate.

Moisey and Rees[15] described the results of a TURP in 22 men with a history of CVA, including two who also had Parkinson disease. Age ranged from 58 to 93 yr.

Staskin et al[17] performed a TURP in 36 Parkinson patients. Comparing this group with 14 unobstructed patients, risk factors for post-TURP incontinence were considered.

3.3.2 Endoscopic treatment of urethral strictures

Endoscopic treatment of urethra strictures was reported in three studies. The underlying neurological disease was SCI in almost all men.

In the study of Cornejo-Dávila et al[11], an endoscopic internal urethrotomy was performed in 12 SCI patients who mentioned any difficulty in IC and had a urethroscopically confirmed bulbar urethral stricture of ≤10 mm. A single cut at 12 o'clock with a conventional straight blade was performed. Two weeks after the procedure, the 16-Fr silicone Foley catheter was removed and IC with the same intervals was resumed.

Krebs et al[12] identified 105 men who used IC for bladder evacuation and had urethral strictures. This group included 99 SCI patients, four patients with spina bifida, and two patients with MS. An endoscopic internal urethrotomy was performed if there were intractable difficulties with IC with an increased risk of urinary retention as a result of impaired catheter passage through the urethra and a confirmed urethral stricture by a retrograde uretrography. This was the case in 38 men, in whom the underlying neurological disease was not further specified. A cold knife incised the stricture at 12 o'clock. If there was no bleeding, the catheter was removed after 24 hours.

Perkash[14] performed endoscopic neodymium:YAG contact laser urethrotomy in 42 SCI patients with strictures approximately 1-4 cm (<2 cm in 39 patients). The stricture was identified through a 23F cystoscope, and a guide wire was passed through the stricture. A contact laser chisel probe, 2.5 or 3.5 mm, screwed at the end of a semirigid fiber was used for endoscopic laser ablation. To achieve complete ablation, the fibrous tissue was vaporized circumferentially. The catheter was removed the next day.

3.3.3 Bladder neck resection

Fourteen BNRs in SCI patients were described in the study of Elsaesser and Stoephasius[16]. When an optically prominent obstruction in the bladder neck was revealed by a cystoscopy, the sclerotic ring was resected between 3 and 9 o'clock or full circle.[16]

3.4 RESULTS ON OUTCOME

The outcome measures are summarized in Table 2. None of the studies measured the pad use to obtain an estimate of UI severity, and none of the studies reported on renal function. We added two non-prespecified outcome measures: "recurrence of anatomic BOO" and "definition of success of intervention used by the study".

3.4.1 Primary outcome of TURP

Two Parkinson patients with overflow UI became dry, and UI persisted in the cases with urge UI.[17] Most of the patients (5/6) with abnormal sphincter control in preoperative urodynamic study became incontinent after TURP. Just one out of 24 patients who had normal sphincter control became incontinent.[17] De novo UI after TURP was reported in patients with Parkinson[17] in contrast to the study of Roth et al[10]. In this study, UI was resolved or improved or persisted after TURP, and de novo UI was not seen.[10]

Moisey and Rees[15] observed a regained normal micturition control in 16 (73%) out of 22 CVA patients. Han et al[13] (CVA patients) and Elsaesser and Stoephasius[16] (SCI patients) did not report the outcome on continence.[13,16] The latter authors considered the outcome of TURP good or improved in 16 out of 21 patients, with a postvoided residues of <100 or <200 ml, respectively.[16] No urodynamic data for CVA patients were provided.[13,15]

3.4.2 Primary outcome of endoscopic treatment of urethral strictures

UI was not observed in the three studies.[11,12,14] Cornejo-Dávila et al[11] and Krebs et al[12] mentioned that IC was restarted in all patients after endoscopic urethrotomy. The study population of Krebs et al[12] needed one to five procedures. The possibility of adequate voiding after laser ablation was seen in 39 of 42 patients (93%). The pre- or postoperative way of bladder empting (IC or spontaneous voiding) was not reported.[14]

3.4.3 Primary outcome of BNR

A postvoid residue of <100 ml could be obtained in 11/14 SCI patients after one or more procedures, while the procedure failed completely in three patients.[16]

TABLE 2. Primary and secondary outcome measures

		Primary outcomes		Secondary outcomes						
Study	**Type of NU study population**	**Degree of incontinence**	**(Non)invasive urodynamics and bladder evacuation**	**Quality of life**	**Adverse effect after treatment**	**Surgical outcome measures**	**Renal function**	**Socio-economic measures**	**Other: recurrence of anatomic BOO**	**Other: definition of success used in the study**
		Anatomic BOO due to BPH								
Roth et al (2009)	Parkinson Disease	-Preoperative urge urinary incontinence in 10/23 (43%) → Postoperative restoration of continence in 5/10; improvement in 3/10; no de novo urinary incontinence. -Preoperative indwelling catheter in 14/23 (61%) → Postoperative restoration of voiding in 9/14	In the 9 patients who were voiding preoperatively a significant increase in maximum flow rate and voided volume and a significant decrease in IPSS, daytime frequency and nocturia was seen postoperative. Maximum flow rate median 5→15 Voided volume median 110→330 IPSS median score 19→7 Daytime frequency median 8→5 Nocturia median 4→2	IPSS QoL (*n*=9) preoperative median 4 (IQR 2–5) postoperative median 2 (IQR 1–2), *P*=0.026	NR	NR	NR	NR	NR	Success was defined as complete urinary continence, normalization of urinary frequency (<8 micturations per 24 h) and no further need of IC or indwelling catheter. -In 16/23 (70%) patients TURP was successful
Han et al (2014)	CVA	NR	Not specified for CVA patients (CVA, older age, diabetes and preoperative antimuscarin drug uses are possible risk factors of persistent voiding dysfunction after TURP)	Not specified for CVA patients (IPSS QoL postoperative higher in non-medication group)	Not specified for CVA patients (urethra strictures 21/372, bladder neck stenosis 4/372, stress urinary incontinence 6/372)	Not specified for CVA patients (no significant difference in operation time between non- and medication group)	NR	NR	Not specified for CVA patients (urethra strictures 21/372, bladder neck stenosis 4/37)	NR

TABLE 2. Continued.

		Primary outcomes		Secondary outcomes						
Study	**Type of NU study population**	**Degree of incontinence**	**(Non)invasive urodynamics and bladder evacuation**	**Quality of life**	**Adverse effect after treatment**	**Surgical outcome measures**	**Renal function**	**Socio-economic measures**	**Other: recurrence of anatomic BOO**	**Other: definition of success used in the study**
Moisey and Rees (1978)	CVA, including *n*=2 with CVA and Parkinson Disease	-Preoperative incontinence rate 3/22 → Postoperative incontinence rate 6/22 (7 became continent after strict bladder training and using anal plug electrode continence devices)	Regained normal micturition control in 16/22 patients; 6/22 patients had incontinence and required an indwelling catheter or an incontinence appliance	NR	NR	NR	NR	Inpatient days: 5-9 d in 8; 10-15 d in 6; >25 d in 8	NR	NR
Statskin et al (1988)	Parkinson Disease	-Preoperative incontinence rate 6/36 (4/36 urge and 2/36 overflow) → Postoperative incontinence rate 10/36 (kept urge incontinence 4/6, de novo urge urinary incontinence 6/30)	Urodynamics: 26/36 (72%) showed normal voluntary sphincter control preoperative; preoperative 2 were incontinent and became postoperative continent; 23/24 kept continent postoperatively; postoperative 5/6 patients who were continent preoperatively with abnormal voluntary sphincter control became incontinent; 1/4 patients with incontinence and abnormal voluntary sphincter control preoperative became continent postoperative	NR	NR	NR	NR	NR	NR	NR

TABLE 2. Continued.

		Primary outcomes		Secondary outcomes						
Study	**Type of NU study population**	**Degree of incontinence**	**(Non)invasive urodynamics and bladder evacuation**	**Quality of life**	**Adverse effect after treatment**	**Surgical outcome measures**	**Renal function**	**Socio-economic measures**	**Other: recurrence of anatomic BOO**	**Other: definition of success used in the study**
		Anatomic BOO due to urethral strictures								
Perkash (1997)	SCI	NR	Adequate voiding after laser ablation was seen in 93%of the patients.	NR	-Treatment failure (*n*=1) -Urinary retention 5 d postoperative who required a single catheterization at home (*n*=1)	-Operation time: mean 25.6 min (range 10-50) -Blood loss: estimated 25-50 ml -Perioperative complications: problems to define the urethral opening and resulting in extravasation (*n*=2), loss of the crystal tip (*n*=1)	NR	1 Catheter day	3/42 (7%) had successful reinterventions with the contact laser. (during mean 28.2 mo follow-up)	Success was defined as the possibility of adequate voiding. ● 39/42 (93%) was successful.
Cornejo-Dávila et al (2017)	SCI	NR	After endoscopic urethrotomy all 12 patients restarted IC.	NR	NR	NR	NR	14 Catheter days	No recurrence 1 yr after endoscopic urethrotomy.	NR
Krebs et al (2015)	Underlying NU not specified (mostly SCI, could be spina bifida, MS)	NR	After endoscopic urethrotomy all 38 restarted IC.	NR	14/38 (37%) patients required more than one (2-5) urethrotomy due to recurrence.	NR	NR	1 Catheter day	-14/38 ≥ 1 redo-urethrotomy -38/38 radiological evidence recurrent stricture, median 14 yrs follow-up	Success was when IC was possible. -Preoperative IC was not possible in 38 patients; after 1-5 procedures IC was possible in all patients.

TABLE 2. Continued.

		Primary outcomes		Secondary outcomes						
Study	**Type of NU study population**	**Degree of incontinence**	**(Non)invasive urodynamics and bladder evacuation**	**Quality of life**	**Adverse effect after treatment**	**Surgical outcome measures**	**Renal function**	**Socio-economic measures**	**Other: recurrence of anatomic BOO**	**Other: definition of success used in the study**
		Anatomic BOO due to BPH, or bladder neck sclerosis, or meatus stenosis								
Elsaesser and Stoephasius (1972)	SCI	NR	Outcome classified as: good with sterile urine, good=RU <100 ml, improved=RU 100-200 ml, or not improved. -TURP: good with sterile urine 3/21, good 9/21, improved 4/21, not improved 5/21 -BNR: good with sterile urine 3/14, good 8/14, not improved 3/14	NR	TURP: perform post-resections of apical residues (*n*=2/21) BNR: 3/14 failed completely (1 died of urosepsis, 2 received external sphincterotomy)	NR	NR	NR	NR	Achieve regulated vesical function, not further defined. -Not clarified.

BNR = bladder neck resection; BOO = bladder outlet obstruction; BPH = benign prostate hyperplasia; CVA = cerebrovascular accident; IC =intermittent catheterization; IQR = interquartile range; MS =multiple sclerosis; NR =not reported; NU =neuro-urological; QoL = quality of life; RU =residual urine; SCI = spinal cord injury; TURP = transurethral resection of the prostate

3.5 SUBGROUP ANALYSES

A subgroup analyses was not possible to perform or contributive. The studies included a small number of patients with different types of anatomic BOO, intervention, and underlying NU pathology.

3.6 Risk of bias assessment

The risk of bias assessed by the Cochrane Risk of bias Assessment Tool and confounding factors was classified high for the two comparative studies. The included studies were assessed as having a high or unclear risk of bias (Figure 2).

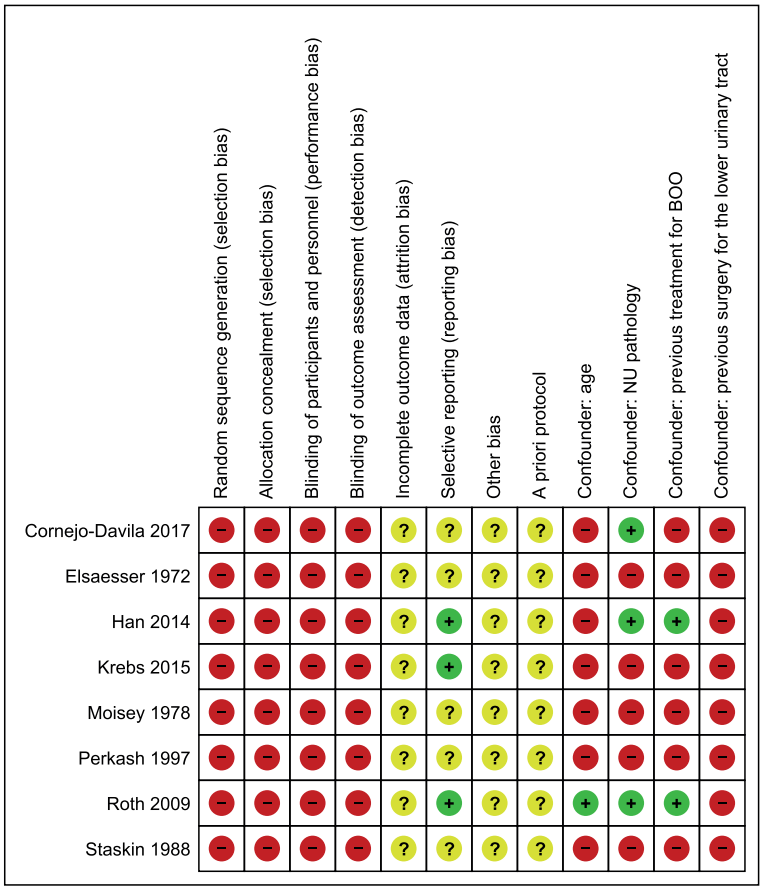

FIGURE 2. Risk of bias summary.

+ = low risk of bias; ? = unclear risk of bias; - = high risk of bias; BOO = bladder outlet obstruction; NU = neuro-urological.

3.7 DISCUSSION

3.7.1 Principal findings

To our knowledge, this is the first review with the focus on surgical management of anatomic BOO in NU patients. The identified surgical treatments were TURP in patients with Parkinson, CVA or SCI, endoscopic treatment of urethral stricture by laser ablation or urethrotomy (mainly in SCI patients), and BNR in SCI patients. The results of TURP in the different types of NU patients varied. De novo UI after TURP in Parkinson patients ranged from 0% to 20%.[10,17] Bladder function had improved after TURP in 76% of SCI patients, defined as postvoiding residue <200 mL.[16] In CVA patients, poorer results on bladder function were seen in case of more severe neurological impairment.[15] Additionally, CVA appeared to be a risk factor of persistent voiding dysfunction and continued medical therapy after TURP.[13] Good results were seen in BNR and endoscopic urethrotomy studies in SCI patients. Both laser ablation and cold knife urethrotomy resulted in restarting IC or adequate voiding. However, studies with a follow up of >1 yr showed that one or more reinterventions due to recurrence were sometimes necessary.[12,14]

3.7.2 Interpretations of findings

First of all, our interpretations are based on a limited number of included studies with a low level of evidence. The surgical outcome of TURP in NU patients may be highly variable and includes persistent or de novo UI, regained normal micturition control, and urinary continence. A urodynamic study could have a predictive value. Staskin et al[17] described an association between postoperative continence and the degree of voluntary sphincter control in Parkinson patients. In NU patients, an invasive urodynamic study is necessary to determine the exact type of neurogenic LUT dysfunction, recommended by the European Association of Urology guidelines.[2,5] A recent systematic review and meta-analysis reported a significant association between preoperative urodynamically proven BOO and better surgical outcome after TURP.[18] However, this was not specified for NU patients. If a urodynamic study is of value in non-NU patients it will definitely be important for NU patients in order to distinguish a functional BOO from an anatomic BOO.

IC is part of regular treatment of NU patients who cannot effectively empty their bladders. It may however cause a urethral stricture, which in turn may necessitate a surgical intervention. The presentation and management of a urethral stricture is less uncertain in comparison with BPH in NU patients. The presence of a urethral stricture should be assessed when inability or difficulty with IC occurs. Repeated urethral dilation or endoscopic urethrotomy or urethroplasty are possible initial treatments,

especially for short bulbar strictures, according to the American Urological Association guidelines.[19] Repeated urethral dilatation and endoscopic urethrotomy (cold knife or laser incision) have similar outcomes. Better outcome but higher morbidity is seen in urethroplasty.[19] Nonetheless, in patients who are not candidates for urethroplasty, endoscopic urethrotomy should be followed by at least 4 mo of IC to maintain urethral patency and reduce the recurrence rate.[19] Most of the NU patients already perform IC.

Endoscopic reinterventions in the included studies were all successful.[12,14] The American Urological Association guideline recommends a urethroplasty when a urethral stricture treated with urethrotomy recurs.[19] This recommendation is based on a retrospective study without NU patients, which showed an association between repeat transurethral manipulation of urethral strictures and increased complexity of the stricture, complicating definitive urethroplasty.[20] To our knowledge, no study discussing the results of urethroplasty after a recurrent urethral stricture of an endoscopic treatment in NU patients is available. In contrast to non-NU patients, even though the risk of strictures remains, IC is necessary in the management of neurogenic LUT dysfunction and will be continued either after urethrotomy or urethroplasty.

Good results of BNR were seen in 11/14 SCI patients with a cystoscopically observed sclerotic ring.[16] In two men, successful outcome was obtained only after a transurethral external sphincterotomy after two failed BNRs. This may indicate that a cystoscopy insufficiently discriminates between anatomic and functional BOO.

3.7.3 Implication for research and clinical practice

The available data, presented here, are insufficient to determine the optimal practice in the surgical treatment of anatomic BOO in NU patients. A urodynamic study should not lack in the work-up of BOO in NU patients. In patients with inability or difficulty with IC, the presence of a urethral stricture should first be assessed. Implications of the neurological bladder dysfunction on the surgical outcome of anatomic BOO cannot be determined in our review. Future studies should compare different surgical and medical therapies of benign prostatic obstruction in NU patients and focus on possible predictors of the outcome, especially concerning UI. In addition, optimal treatment of urethral strictures has yet to be determined.

3.7.4 Strengths and limitations

Our study gives an overview of the current literature on the surgical treatment of anatomic BOO in NU patients. Despite the use of strict guidelines when conducting this systematic review, several limitations should be addressed. First, all included studies were retrospective and had poor scientific quality. Second, the limited number

of included studies, and the small number and heterogeneity of the patients between and in the studies made a subgroup analysis impossible. None of the studies compared interventions in the management of the same type of anatomic BOO. Finally, different terminology and parameters of outcome were used. A recently published systematic review found a considerable heterogeneity in outcome parameters to report of surgical interventions in NU patients.[21] To improve the quality of studies and draw meaningful conclusions, standardized terminology and definitions of outcome in accordance with the International Continence Society should be used.[3,22]

4. CONCLUSIONS

The eight included studies, with relatively poor scientific quality, demonstrated outcomes of various surgical approaches in different types of anatomic BOO and in heterogeneous NU study populations. Therefore, identifying the optimal practice in surgical treatment of these NU patients was not possible in this review with limited availability of eligible studies. However, our study provides an overview of the current literature on the surgical treatments. Future studies in NU patients with anatomic BOO should focus on the outcome of the surgical intervention for continence and preoperative noninvasive and invasive urodynamic measurements. Furthermore, standardized terminologies and definitions of outcomes should be used.

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SUPPLEMENTARY MATERIAL: SEARCH STRATEGY

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('neurogenic bladder'/exp OR (('bladder disease'/exp OR 'nocturia'/de OR 'micturition disorder'/de OR 'urinary hesitancy'/de OR 'urine incontinence'/exp OR 'urine retention'/de OR prostatism/de OR 'impaired bladder emptying'/de OR 'postvoid residual urine volume'/de OR 'lower urinary tract symptom'/exp) AND ('neurologic disease'/de OR 'Parkinson disease'/de OR 'multiple sclerosis'/de OR 'spinal dysraphism'/exp OR 'spinal cord disease'/exp OR 'cerebrovascular accident'/exp OR 'brain infarction'/exp OR 'brain ischemia'/exp)) OR (((neuroge* OR neurolog* OR neuropath* OR spastic*) NEAR/6 (bladder* OR vesical* OR urogenit*)) OR nlutd OR nlutds OR ((neurogen* OR neurologic* OR parkinson* OR (multiple NEAR/3 sclerosis) OR (spina* NEAR/3 (dysraphis* OR bifida OR disease OR injur*)) OR stroke OR cva OR (cerebrovascula* NEAR/3 (accident* OR event*)) OR ((brain OR cerebral*) NEAR/3 (infarct* OR ischem* OR ischaem*))) AND (nocturia OR post-void* OR postvoid* OR (micturition NEAR/3 disorder*) OR hesitanc OR incontinence OR retention OR prostatism OR (impaired NEAR/3 empty*) OR LUTS OR LUTD OR LUTDs OR ((dysfunction* OR symptom* OR deficien* OR overactiv* OR underactiv* OR hyperactiv* OR hypoactiv* OR hypoton* OR hyperton*) NEAR/6 (lower-urinar*-tract* OR detrusor* OR urethra* OR bladder* OR void*))))):ab,ti) AND ('bladder obstruction'/exp OR 'urethra obstruction'/de OR 'obstructive uropathy'/de OR 'bladder neck stenosis'/de OR 'urethra stenosis'/de OR 'urinary tract obstruction'/de OR 'prostate hypertrophy'/de OR (((vesical* OR bladder* OR urethr* OR prostat* OR infravesical* OR bph OR urinary-tract* OR uropath*) NEAR/6 (obstruct* OR stenos*)) OR (obstruct* NEAR/6 flow NEAR/6 urin*) OR (prostat* NEAR/3 (hypertroph* OR hyperplas*))):ab,ti) AND ('surgery'/de OR 'surgical technique'/de OR 'urologic surgery'/exp OR 'surgery':lnk OR (surger* OR resect* OR incision* OR prostatectom* OR urethrotom* OR urethroplast* OR reconstruct* OR replace* OR turp OR bni OR diversion* OR conduit* OR strictur*):ab,ti) NOT (child/exp NOT adult/exp) NOT (female/exp NOT male/exp) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

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PART II

Outcomes of surgical treatment in functional urology


2.1

CHAPTER 3

Long-term follow-up of bladder outlet procedures in children with neurogenic urinary incontinence

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SUMMARY

Introduction: Achieving continence in children with neurogenic sphincteric incompetence is a challenge. Awareness of the long-term outcome in this young patient population is important. In the past 25 years, the study institution has built experience in bladder outlet procedures such as bladder neck sling and bladder neck reconstructions.

Objective: The objective of this study was to evaluate the long-term outcome on continence and re-intervention rate of bladder outlet procedures in children with neurogenic urinary incontinence in the study institution.

Design: All children who underwent a bladder neck procedure between 1992 and 2017 at the study institution were retrospectively reviewed. Continence at the end of follow-up was the primary endpoint, defined as 'dry' when there was an interval of a minimum of 4 h without urinary leakage. Non-parametric tests were used for statistical analysis.

Results: During this 25-year period, a total of 60 children underwent a bladder outlet procedure, either a bladder neck sling ($n = 43$) or a bladder neck reconstruction ($n = 17$). The median age at surgery was 11.6 years (interquartile [IQR] 7.8-13.9). Concomitant surgery consisted of bladder augmentation in 80% and continent catheterizable urinary channel in 97% of children. Dry rate within 1 year was 38%. After a median follow-up of 10.4 years (IQR 6.5-15.5), 77% of all children were dry. Twenty-five children (42%) needed one or more re-interventions, including redo of the bladder outlet procedure, other type of outlet procedure, bulking agents, bladder augmentation, and bladder neck closure.

Discussion: This study confirms that achieving continence is a challenge. The inconsistent use of the definition of urinary continence creates confusion in the literature and makes comparison of outcome with other studies difficult. Openness of (long-term) results in achieving urinary continence is important and helpful for future patients.

Conclusion: On the long term, the majority of children with neurogenic urinary incontinence were dry after a bladder outlet procedure, but a considerable number of patients had a re-intervention. The initial outcome on continence was slightly disappointing. Reporting long-term results is essential and helpful for patient counseling.

1. INTRODUCTION

The main challenging urological goals in children with neurogenic bladder dysfunction are to preserve the upper urinary tract function and to achieve urinary continence.[1-3] Management should focus on ensuring bladder emptying, attaining safe bladder storage pressure and capacity, and adequate sphincteric outlet resistances.[1-3] A urodynamic evaluation is necessary to characterize the cause of urinary incontinence.[4-6] Surgical therapy could be considered when non-surgical therapy such as anticholinergic medications and intermittent catheterization fails. The appropriate surgical management must be determined individually for each child based on urodynamic findings.[1,2,4-6]

The etiology of urinary incontinence secondary to neurogenic sphincteric deficiency includes myelomeningocele (MMC), sacral agenesis, acquired spinal cord tumor, iatrogenic injury, and trauma.[5] Surgical options that have been developed to increase bladder outlet resistance in the treatment of neurogenic sphincteric incompetence are bladder neck sling, bladder neck reconstruction, artificial urinary sphincter (AUS), and injection of bulking agents.[1,2,4-6] These bladder outlet procedures can be combined with bladder augmentation to improve bladder capacity and/or continent catheterizable urinary channel for catheterization.[1,2,4,5] Unfortunately, reports on long-term results are scarce.

In the past 25 years, the study institution has built experience in bladder outlet procedures such as bladder neck sling and bladder neck reconstructions. Based on clinical experience, continence on the long term can be achieved with both bladder neck reconstruction and bladder neck sling, but a re-intervention for persistent incontinence is not exceptional. This study aimed to evaluate the long-term outcome on continence of bladder outlet procedures in children with neurogenic urinary incontinence at the study institution. Furthermore, the re-intervention rate and complication rate were evaluated.

2. MATERIAL AND METHODS

2.1 Study population

Children (age <18 years) with neurogenic urinary incontinence secondary to sphincteric deficiency who underwent a bladder outlet procedure (bladder neck reconstruction or bladder neck sling) between 1992 and 2017 at the study institution were eligible for inclusion. Children with a postoperative follow-up of less than 1 year were excluded. The principles of Helsinki Declaration were followed in lieu of formal ethics

committee approval. The etiologies of neurogenic urinary incontinence were MMC, VACTERL-associated (vertebral defects, anorectal malformations, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities) cause, and sacrococcygeal teratoma. The individual patients' medical charts were retrospectively reviewed. Primary outcome was the postoperative continence rate at the last outpatient visit. Urinary continence was defined as 'dry' when there was a patient-reported interval of a minimum of 4 hours without urinary leakage between voiding or intermittent catheterizations. Secondary outcomes were continence within 1-year postoperative, re-interventions, and complications.

2.2 Surgical procedure

The purpose of the bladder outlet procedure was to increase the bladder outlet resistance. The bladder outlet procedure was often combined with the creation of a continent catheterizable urinary channel, most commonly an appendicovesicostomy. All patients were analyzed pre-operatively with urodynamic study and cystoscopy. Pre-operatively, a low-pressure urinary reservoir with sufficient capacity, using anticholinergics, was aimed for. In this practice, it is of standard care to start with anticholinergics and intermittent catheterization in children with MMC immediately after birth. A bladder outlet procedure was combined with bladder augmentation if a low compliant and/or a small capacity bladder insufficiently responsive to anticholinergics or botulinum toxin A was seen on urodynamic study interpreted by the urologists and urodynamic physician. In general, in the study institution a bladder compliance reported of <15 mL/cmH_2O on urodynamic study was defined as low compliant, and a bladder capacity of <50% of the expected bladder capacity calculated with the formula ([age {years} + 1] x 30 mL) was defined as low capacity.

Before the bladder outlet procedure, the anatomy of the bladder outlet was evaluated by cystoscopy at the time of the surgery. In this study, bladder outlet procedures were divided in two types: bladder neck reconstruction and bladder neck sling. The choice of technique depended on the preference of the surgeon. A bladder neck reconstruction was performed using one of the three techniques described by Jones et al[7], Pippi Salle[8], or Dees[9]. The results of those techniques were chosen to be merged because they all increase the bladder outlet resistance by lengthening and narrowing the urethra with tubularization of the trigone. The bladder neck sling procedure was based on coaptation, elevation, and narrowing of the urethra by suspension of the bladder neck by placing an autologous rectus fascial strip around the bladder neck and fixing the ends to the pubic symphysis.[10]

2.3 Follow-up

All patients had an outpatient visit within 1 year postoperatively combined with a urodynamic study. Depending of the underlying disease, the outpatient visits varied in interval at the urologist or pediatrician. During follow-up visits, all patients were asked about (in)continence, and patient-reported dry interval was noted. If severe incontinence was reported, a urodynamic study was conducted, and when indicated, a re-intervention was planned. All patients underwent a renal ultrasound investigation. The time interval between bladder outlet procedure and re-intervention of the bladder neck was determined. In case of usage of bulking agents, two types were used: dextranomer/hyaluronic acid copolymer or polydimethylsiloxane. Complications >30 days postoperatively were categorized into bladder stones, problems with catheterization of the continent catheterizable urinary channel, or other complications. The duration of follow-up was defined as the time from the date of surgery to the date of the last outpatient visit.

2.4 Statistical analysis

Information about urinary leakage, frequency of intermittent catheterization, demographic data, and data on medical history were retrospectively collected from patients' medical charts. Descriptive statistics are presented as median (interquartile range [IQR]), frequency, and percentiles. The chi-squared test and the Mann-Whitney U test were used to analyze categorical and continuous variables, respectively. The occurrence of a re-intervention over time is distributed in a Kaplan-Meier curve. A two-sided *P*-value of <0.05 was considered significant. Statistical analyses were performed using SPSS, version 24.0 (IBM Corp., Armonk, NY).

3. RESULTS

3.1 Study population

A total of 60 patients underwent bladder outlet procedures from 1992 to 2017 at a median age of 11.6 (IQR 7.8-13.9) years. Thirty-five (58.3%) patients were female. The etiology of neurogenic urinary incontinence was predominantly (91.7%) MMC. In Table 1 the patient characteristics are shown. Forty-three (71.7%) patients underwent a bladder neck sling procedure and 17 (28.3%) a bladder neck reconstruction. Concomitant surgeries included a continent catheterizable urinary channel in 58 (96.7%) patients and bladder augmentation in 48 (80.0%) patients. Five patients had a urological history of bulking agents (before bladder neck sling $n = 3$ and before bladder neck reconstruction $n = 2$).

TABLE 1. Characteristic presented as number (%) or median (interquartile range).

	Total, *n* = 60	**BNS, *n* = 43**	**BNR, *n* = 17**	***P*-value**
Gender				
- Female	35 (58.3%)	31 (72.1%)	4 (23.5%)	$P < 0.001$[a]
- Male	25 (41.7%)	12 (27.9%)	13 (76.5%)	
Median age at operation, yrs (IQR)	11.6 (7.8-13.9)	11.8 (8.5-14.1)	10.4 (7.6-12.5)	$P = 0.279$[b]
Median follow up, yrs (IQR)	10.4 (6.5-15.5)	11.2 (7.5-18.2)	8.9 (6.1-15.1)	$P = 0.305$[b]
Etiology				
- MMC	55 (91.7%)	41 (95.4%)	14 (82.4%)	$P = 0.086$[a]
- VACTERL association	4 (6.7%)	1 (2.3%)	3 (17.6%)	
- Sacrococcygeal teratoma	1 (1.7%)	1 (2.3%)	-	
Concomitant surgery:				
- Continent catheterizable channel	58 (96.7%)	41 (95.3%)	17 (100%)	$P = 0.366$[a]
- Bladder augmentation	48 (80.0%)	33 (76.7%)	15 (88.2%)	$P = 0.316$[a]
- Ureteral reimplantation	5 (8.3%)	3 (7.0%)	2 (11.8%)	$P = 0.545$[a]

Bladder neck sling (BNS); bladder neck reconstruction (BNR).
[a] Chi-squared test
[b] Mann-Whitney U test

3.2 Continence outcome

Within 1 year postoperatively, 23 (38.3%) patients were dry, 15 after bladder neck sling and 8 after bladder neck reconstruction ($P = 0.38$, Table 2).

TABLE 2. Continence outcome presented in number (%) and numbers specified for gender.

	Total	**BNS**	**BNR**	***P*-value**
Dry rate <1yr follow-up	23/60 (38.3%)	15/43 (34.9%)	8/17 (47.1%)	$P = 0.382$[a]
Men, $n = 25$		5/12	6/13	$P = 0.821$[a]
Women, $n = 35$		10/31	2/4	$P = 0.482$[a]
Dry rate >1yr follow-up	46/60 (76.7%)	33/43 (76.7%)	13/17 (76.5%)	$P = 0.982$[a]
Men, $n = 25$		10/12	9/13	$P = 0.409$[a]
Women, $n = 35$		23/31	4/4	$P = 0.247$[a]

Bladder neck sling (BNS); bladder neck reconstruction (BNR).
[a] Chi-squared test

After a median follow-up of 10.4 (IQR 6.5-15.5) years, 46 (76.6%) patients were dry (minimum of 4-hours interval) with or without additional continence procedures. Thirteen (21.7%) patients were not dry (urethral leakage $n = 6$, leakage from urinary conduit $n = 6$, urinary leakage from both $n = 1$), and one (1.7%) patient, who had a bladder neck sling procedure, was dry with a 3-h interval. The majority of incontinent patients accepted the situation. The initial bladder outlet procedure of the dry patients was bladder neck sling in 33 of 43 patients and bladder neck reconstruction in 13 of 17 patients ($P = 0.98$, Table 2). Dryness rate within 1 year and dryness rate on the long term did not differ between the types of bladder outlet procedure, also when specified for gender (Table 2).

3.3. Re-interventions

After a median follow-up of 10.4 years, 41.7% (25/60) of the study population received a re-intervention of the bladder neck procedure. Within this group, the median time between bladder outlet procedure and re-intervention was 1.0 (IQR 0.6-2.6) year. The Kaplan-Meier curve presents the time until re-intervention during follow-up (Figure 1). Most re-interventions were carried out because of a bladder outlet problem, except in two patients. In one, a bladder augmentation was applied because of a poor bladder compliance. Another required a bladder augmentation (combined with redo of the bladder neck sling) for a de novo therapy-resistant detrusor overactivity. The re-interventions included redo of the bladder outlet procedure, other type of outlet procedure than the initial one, bulking agents, bladder augmentation, and bladder neck closure. The various re-interventions of the bladder neck and the outcome on continence are specified in Figure 2. In 58.3% (35/60) of the study population, a re-intervention was not necessary; 31 patients were dry, and four patients considered the incontinence acceptable.

3.4 Complications

After a median follow-up of 5.1 (IQR 3.7-9.2) years, 23 patients were treated for a bladder stone. The occurrence rate of a bladder stone was comparable between the types of bladder outlet procedures. All patients with bladder stones had a continent catheterizable urinary channel, and 20 patients had an augmented bladder. In eight patients the bladder stones recurred.

After a median follow-up of 1.2 (IQR 0.8-5.4) years, the continent catheterizable urinary channel was surgically revised because of problems with catheterization in 15 patients, nine with a bladder neck sling and six with a bladder neck reconstruction. There was no difference between the two types of bladder outlet procedures.

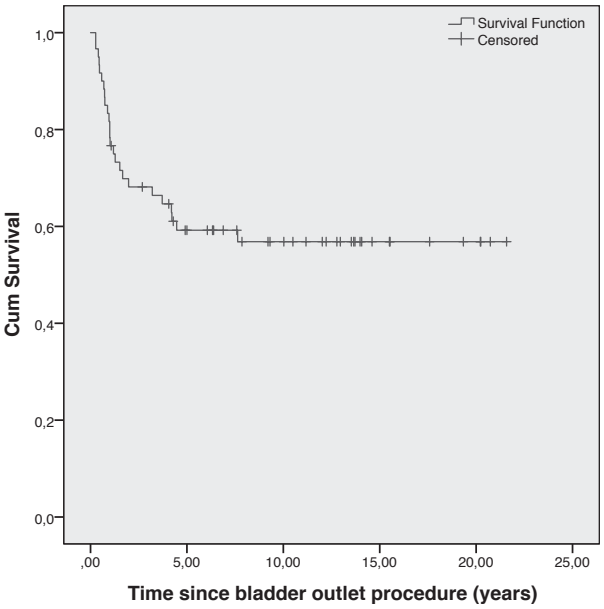

FIGURE 1. Re-intervention-free survival after bladder outlet procedure distributed in a Kaplan-Meier curve.

Two patients had an abdominal laparotomy (32 and 40 months postoperatively, respectively) on suspicion of a bladder perforation. The type of bladder outlet procedure was different, but both underwent concomitant surgery including a bladder augmentation and a continent catheterizable urinary channel.

4. DISCUSSION

Although techniques and insights have changed over the years, achieving continence in children with neurogenic sphincteric incompetence is still a challenge. The choice of a bladder outlet procedure with or without concomitant surgery such as bladder augmentation and continent catheterizable urinary channel is influenced by the patient's needs, gender, bladder function, and the surgeon's preference. Long-term outcome of these surgical procedures, especially in view of the young age of these patients, is important, but unfortunately, reports on this aspect are sparse. In this retrospective cohort study, the continence results within 1 year after a bladder neck sling and bladder neck reconstruction were rather disappointing (dry: 38 %). On the long term (median follow-up of 10.4 years), continence rate was modest to good (dry: 77%), although re-intervention was required in 42% to achieve this result.

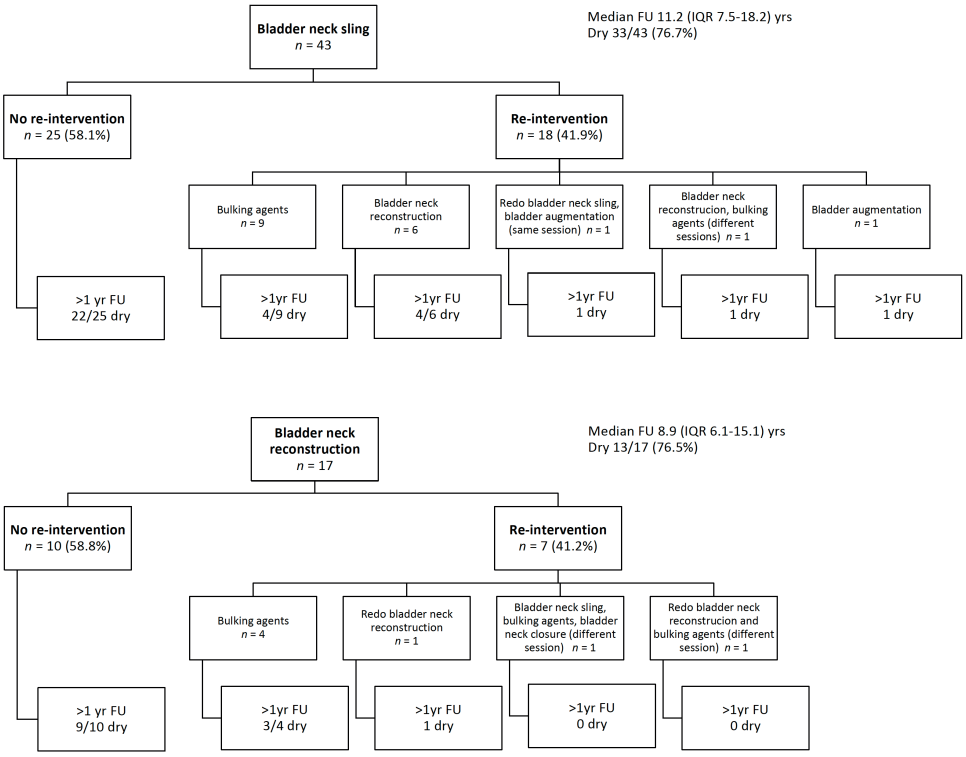

FIGURE 2. Long-term results on dryness with or without reintervention. FU, follow-up; IQR, interquartile range.

Comparison with other studies is difficult because of the different modifications of surgery techniques used, alternated concomitant surgery, small number of patients analyzed, varying time of follow-up (the majority short term), and different definitions of urinary continence. Reported continence rates after bladder neck sling procedure ranged from 40% to 100% and after a bladder neck reconstruction from 50% to 88%. However, follow-up was short in most of these studies.[5] The long-term results on continence after bladder neck sling (77%) and bladder neck reconstruction (77%) are within this range. For both the types of procedure, re-intervention was necessary in more than 40% of cases (42% bladder neck sling and 41% bladder neck reconstruction). Reported re-intervention rates in other series are scarce, amounting to 3%-40% for bladder neck sling[11-13] and 12%-83% for bladder neck reconstruction[5,14]. A summary of the literature used for this discussion is given in Table 3.

The inconsistent use of the definition of urinary continence creates confusion in the literature.[15] In some studies cured and improved patients are grouped together; others use vague terms such as 'social continence'.[14,15] Urinary continence was defined as an interval of a minimum of 4 h without urinary leakage between voiding or intermittent catheterizations. Besides outcome on continence, another important outcome is patient's satisfaction. Completely dry will not automatically be proportional to a patient's satisfaction. In the follow-up, it was not of standard care to use validated questionnaires to measure patient's symptoms or quality of life. Hence, it was impossible to evaluate the outcome of surgical (re)intervention on urinary continence in relation to patient-reported outcome and effect on the quality of life.

In this series, more bladder neck sling procedures were performed in females than in males. Ten of 12 males after bladder neck sling became dry at the end of follow-up. Contradictory outcomes on continence in males are described in the literature, ranging from 0% to 87%.[11,12,16] One study presented favorable results on continence (87%), but this was only a small series of 15 boys, and urinary continence was defined as complete 'passive' urinary continence.[12] Injury to the periprostatic neurovascular bundle during the surgery could lead to impotence. Bladder neck sling procedures are not an obvious choice in boys due to unclear results on continence together with the risk of impotence. In boys, a bladder neck reconstruction is chosen to be preferred to minimize damage on the neurovascular bundle of the prostate. A bladder neck sling procedure could possibly give more damage on the posterior side of the bladder neck. Although most literature studies did not report on outcomes of erectile function, one study reported preservation of erectile function after bladder neck sling in four postpubertal males.[16] As the population in whom these interventions are performed is young, retaining sexual function should be a point of attention.

Before the bladder outlet procedure and during follow-up, intravesical pressure, bladder capacity, and compliance should be evaluated with urodynamic studies. Sufficient capacity and adequate compliance are essential to achieve urinary continence and protect the upper urinary tract. In this study, the bladder outlet procedure was combined with bladder augmentation in 80% (n = 48, Table 1) due to insufficient pre-operative response to anticholinergics or botulinum toxin A. During follow-up another two patients required a bladder augmentation. Considering a bladder outlet procedure without bladder augmentation should be based on careful patient selection. Shared decision-making with the patient/parents is important to ensure understanding of the risk of a future re-intervention and the need of committed follow-up.[17]

The injection of bulking agents and AUS are other techniques to increase the resistance of the bladder neck in the treatment of neurogenic sphincteric incompetence. According to the literature, in about one-third of cases, continence can be achieved with bulking agents as primary therapy.[1,18-20] However, deterioration in continence is expected on the long term.[19,20] The exact role, primary or secondary therapy, of this minimally invasive technique in neurogenic sphincteric incompetence seems unclear. In a recently published study by Faure et al, 13 (45%) children with neurogenic sphincteric incompetence, who were primarily treated with bladder neck reconstruction, had become dry with injection of bulking agents.[14] Injections of bulking agents as secondary procedure, after bladder neck sling, resulted in two (7%) dry patients, described by Vocht et al.[21] In this study, bulking agents resulted in continence in four patients after bladder neck sling (44%) and in three (75%) after bladder neck reconstruction (Figure 2). It is worthwhile to consider the injection of bulking agents for relief of mild urinary continence after previous bladder outlet procedure. Of course, the patient/parents should be clearly counseled on the expectations.

The study institution has no experience with AUS in children. Variable continence rates in children with neurogenic urinary incontinence are described in the literature at varying time of follow-up periods. Continence rates reported by Kryger et al[22], Simeoni et al[23], and Catti et al[24] were 56% (mean follow-up 15.4 years), 77% (mean follow-up 5.1 years), and 73% (median follow-up 5.5 years), respectively. Continence results appear independent of age at the time of implantation.[6,22] Better results were described when the AUS is implanted on a non-operated bladder neck.[6,23] Revision rate of long-term experience is 0.03 revisions per patient-year.[4,5] Patients in the neurogenic population are often wheelchair bound; therefore, it is suggested that there is a risk of perineal pressure which could possibly lead to complications. Some considerations should be made before implantation of the AUS in children. The most important are to recognize the general risk of infection and the possible problem of erosion and revision. Other aspects to evaluate are the patient's bladder capacity and compliance, patient's mobility, and previous surgery of the bladder neck. Furthermore, the need of intermittent catheterization is not ruled out after an AUS.

Several limitations of this study must be mentioned. First is the retrospective single-center design of this study and the fact that the medical files in the study institution were digitalized during the period 1992 - 2017. Together, this may have resulted in missing data, such as data retrieved from voiding charts or information about sexual function. Second, data of urodynamic studies were not assessed because the primary outcome was urinary continence and secondarily the re-interventions and complications were

TABLE 3. Summary of the literature used in the discussion.

Study	Follow-up	Type of BOP	Definition of continence	Continence rate[a]	Re-intervention/revision rate[a]
Current study	Median 10.4 years	BNS and BNR	Dryness for a minimum of 4 h interval without urinary leakage between voiding or intermittent catheterizations	BNS 77% (33/43) BNR 77% (13/7)	Re-intervention rate: BNS: 42% (18/43) BNR: 41% (7/17)
Kryger et al[5] 2000 (review)	Varying	BNS, BNR and AUS	Different definitions of urinary continence used	BNS: 40-100% BNR: 50-88% AUS: 76-93%	Revision rate: BNS: 15% BNR: 12-45% AUS: 19-28%
Faure et al[14] 2017	Median 16 years	BNR	'Social continence' dry period lasting ≥3 hours with no urinary leakage during the day and without the necessity of a pad	17% (6/35)	Re-intervention rate: 83% (29/35)
Snodgrass et al[13] 2007	Mean 1.8 years	BNS	1. No or occasional urinary leakage 2. ≤2 pads/day	1. 56% (17/30) 2. 83% (25/30)	Bladder augmentation 3% (1/30)
Castellan et al[12] 2005	Mean 4.2 years	BNS	Complete 'passive' urinary continence for 4-6 h during day and 6-8 h at night	88% (51/58)	Re-intervention rate: 9% (5/58)
Nguyen et al[16] 2001	Unclear	BNS	1. Completely dry 2. No diapers required and performed intermittent catheterizations every 4-6 h to remain continent	1. 14% (1/7) 2. 86% (6/7)	Bladder augmentation 57% (4/7) Bladder neck closure 14% (1/7)
Barthold et al[11] 1999	Mean 2.1 years	BNS	Completely dry during day and night	50% (5/10)	Re-intervention rate: 40% (4/10)
Guys et al[20] 2006	Mean 6 years	Injection of bulking agents[b]	Continent more than 4 h and not requiring incontinence protection during day	33% (16/49)	Second injection 37% (18/49) Third injection 27% (13/49)
Kryger et al[22] 2001	Mean 15.4 years	AUS	Dryness for 4 h between voiding or catheterization, with allowance for small leaks that did not necessitate the use of pads.	56% (18/32)	Revision rate: 56% (18/32)
Simeoni et al[23] 1996	Mean 5.1 years	AUS	Unclear	77% (82/107)	Revision rate: 59% (63/107)
Catti et al[24] 2006	Median 5.5 years	AUS	Dryness for 3 h	73% (32/44)	Removal rate: 20% (9/44) Revision rate: 14% (6/44) Replacement rate: 11% (5/44)

BOP, Bladder Outlet Procedures; BNS, Bladder Neck Sling; BNR, Bladder Neck Reconstruction; AUS, Artificial Urinary Sphincter.

[a] If available presented in numbers.

[b] Type of bulking agent: polydimethylsiloxane.

reviewed. Finally, the heterogenicity in re-interventions and type of bladder outlet procedure could be a source of bias. Unfortunately, the number of patients was too small to investigate in detail the differences in surgical techniques.

Despite the limitations, the strength of this study is the long-term follow-up and the openness of results in achieving urinary continence. Those long-term results are valuable for patient counseling and for creating realistic expectations in patients and parents of the outcome of surgical treatment. Based on these results and the number of patients, it is not possible to state which technique is the most preferred or to indicate outcome predictors. Both would be interesting for future research. Additionally, future studies should use patient-reported outcome measurements to evaluate the effect of surgery on symptoms and the quality of life.

5. CONCLUSION

This study confirms that achieving continence is a challenge in children with urinary incontinence secondary to neurogenic sphincteric incompetence. The number of dry patients after a bladder neck sling and bladder neck reconstruction within 1 year was somewhat disappointing, although long-term moderate-to-good continence rates were noted. However, a considerable number of patients had a re-intervention. Reporting long-term results is essential and helpful for patient counseling.

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CHAPTER 4

Outcome and complications of adjustable continence therapy (ProACT™) after radical prostatectomy: 10 years' experience in 143 patients

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ABSTRACT

Aims: To evaluate our outcomes of the adjustable continence balloons ProACT™ for the treatment of male stress urinary incontinence after radical prostatectomy.

Methods: Between May 2007-August 2016 the ProACT™ was implanted in 143 patients without a history of radiotherapy. Endpoints were patient-reported changes in pad counts and complications. Treatment was considered successful if no pad or just one "security" pad per day sufficed, and improved if daily pad use was reduced by ≥50%.

Results: Incontinence before implantation was mild in 36 (25%), moderate in 57 (40%), and severe in 50 (35%) patients. Complications within 30 days were classified by the Clavien-Dindo classification; eight (5.6%) grade I, three (2.1%) grade II, three (2.1%) grade IIIb, and 129 (90.2%) patients had no complication. Revision was done in 43 (30%) patients. The IPSS quality of life item improved significantly from 5.0 (IQR 4.0-5.0) preoperative to 2.0 (IQR 1.0-4.0) and 1.0 (IQR 0.0-3.0) 6 and 12 months after implantation, respectively. After a median follow up of 56 months (range 28 to 79, $n = 112$), 72 (64%) patients were improved, including 51 (45%) patients were successful. Daily pad use decreased from 3.0 to 1.0 (67% reduction). The median outcome on the Patient Global Impression of Improvement scale was "much better", and 97 (87%) patients perceived improvement.

Conclusions: The minimally invasive ProACT™ device showed a clear beneficial continence outcome in patients with stress urinary incontinence after radical prostatectomy. The majority of the patients were satisfied and perceived improvement ≥50% on daily pad use on the long term.

1. INTRODUCTION

Post prostatectomy urinary incontinence (PPI) is a devastating complication after a radical prostatectomy (RP).[1] In most cases this concerns stress urinary incontinence (SUI) caused by intrinsic sphincter deficiency.[2] The prevalence of SUI after is up to 60%, at varying times after the operation.[3] Usually, SUI has a great negative impact on the patients' quality of life.[2,4] Several approved devices for the surgical treatment for male SUI are available. One of these is the ProACT™ device (Uromedica, Inc., MN) which consists of two periurethrally placed volume-adjustable balloons.[1] The volume of the balloons can be adjusted in an outpatient setting to achieve the optimal balance between voiding pressure and continence.[1] Successful outcome after ProACT™ implantation has been correlated with an increase in urethral resistance and increased maximum urethral closure pressure.[5,6]

Several studies reported a significant reduction of daily pad use and improvement on quality of life index scores with the use of ProACT™. Some studies showed dry or daily pad use improvement rates ranging from 60-92% limited to 12-24 months.[1,7-9] Long term outcomes reported in the literature are hardly available. Three studies with a mixed population of patients with PPI and post transurethral resection of the prostate incontinence with a follow up ranging from 56-58 months showed a 50-66% overall dry rate, defined as "no pad or one security pad",[10,11] or a 4.5% overall dry rate, defined as "no pads".[12]

Quality of life is an important outcome domain in the treatment of urinary incontinence.[13] Multiple-question condition-specific quality of life instruments give access to many components of the condition, but some are extensive and minimally suitable in the standard clinical setting.[13-15] The Patient Global Impression of Improvement (PGI-I) scale is a global index that provides an overall response to an intervention.[13] It is a simple, easy-to-use and easy to interpret tool in clinical practice and research settings.[13-15] The PGI-I scale has been used and/or has been validated for women with SUI,[13] women with urogenital prolapse,[14] men with lower urinary tract symptoms secondary to benign prostatic hyperplasia,[15] and patients with non-urological diseases.[16]

We have been using the ProACT™ device for the treatment of male SUI after RP at our department Urology since May 2007. The aim of this study is to evaluate our results in terms of success, changes in pads use, complications and patient-reported estimates of improvement assessed with the PGI-I scale.

2. PATIENTS AND METHODS

2.1 Study population

We included patients with SUI after RP who had the ProACT™ device implanted between May 2007 and August 2016 after conservative treatment with pelvic floor exercises for 1 year had failed. In all patients the possibility of adjustable continence balloons, male sling, and artificial sphincter were discussed. Patients with an artificial urinary sphincter (AUS) or male sling in situ and those with a history of adjuvant radiotherapy after RP were excluded. Severe SUI and a history of failed and removed urinary incontinence devices (AUS, male sling or ProACT™) were not exclusion criteria. All included patients underwent a cystoscopy (to assess the presence of a stricture) and an urodynamic study.

2.2 Intervention

Initially, the ProACT™ device was implanted percutaneously with the use of a rigid 19F cystoscope and fluoroscopy in the anterior posterior direction. After April 2014 a flexible cystoscope was used. The flexible cystoscope provides retrospective intravesical examination during implantation and the use of it may decrease the amount of bladder neck perforations. Furthermore, a flexible cystoscope causes less friction in the bladder neck than a rigid cystoscope and results in less chance of increased SUI just after placement of the balloons. Two separate titanium ports are placed in the scrotum and connected to each of the balloons, respectively, via a tube. All procedures were performed by the same surgeon (BB) with the patient in lithotomy position mostly under general anesthesia, otherwise under spinal anesthesia. Perioperative intravenous antibiotic prophylaxis consisting of cefazolin and metronidazole was given. In most cases patients were discharged from the hospital on the day of surgery after removal of the transurethral catheter and a successful voiding trial. If the bladder neck was perforated intraoperatively the balloon was still placed ipsilaterally of the perforation but as a rule more laterally than without a perforation. In these patients, the transurethral catheter was removed at day 5 or 7 and oral antibiotics were started at approximately the removal time. After the implantation, patients visited the outpatient clinic every 3-4 weeks. Balloon volume was adjusted with maximal 1 mL per balloon per visit by needle puncture of the subcutaneous port sited in the scrotum. This was done by a specialized nurse or by the surgeon until continence was achieved.

2.3 Design

After obtaining approval by the local ethics committee (MEC-2017-05) all eligible patients were sent an information letter and a three-item questionnaire with a return envelope;

1. The dichotomous question: "Would you recommend ProACT™ to someone else?" to be answered by yes or no.
2. The PGI-I scale: check the number that describes how your condition is now compared to before the ProACT™ implantation: 1. "very much better", 2 "much better", 3. "a little better", 4. "no change", 5. "a little worse", 6. "much worse", 7. "very much worse".
3. The open-ended question: How many pads do you use daily?

Other relevant data were retrospectively retrieved from the individual patients' medical charts. Preoperative evaluation included medical history, anamnestic pad count, voiding diary, American Society of Anesthesiologists (ASA) classes, and International Prostate Symptom Score (IPSS). The severity of urinary incontinence was classified by the anamnestic pad use per day and ranked as mild (1 or 2 pads), moderate (3 or 4 pads) or severe (5 or more pads or use of condom catheter). Postoperative evaluation included anamnestic pad count, IPSS, and complications. Complications within 30 days postoperative were graded using the Clavien-Dindo Classification of Surgical Complications.[17] Failure of the intervention was defined as explantation with or without revision of the ProACT™ device, or as an additional surgical procedure needed because of persistent incontinence (eg, onabotulinumtoxin-A injected in the bladder wall, sacral neuromodulation, bulking agents, male sling, AUS).

Postoperative continence was assessed according to changes in pad counts. The outcome of the treatment was defined as "successful" when the patient was dry (no pad or a single "security pad" per day); as "improved" when ≥50% reduction in daily pad use against preoperative use was reported; and as "little/no improvement" when <50% reduction in daily pad use against preoperative use was obtained. The PGI-I question served to evaluate a patient's perception of improvement on his condition. A lower score on the 7-point scale corresponds with a better condition than before ProACT™ implantation.

2.4 Statistical analysis

Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY). A two-sided *P*-value <0.05 was considered statistically significant. Descriptive statistics are presented as percentages for qualitative variables and median and interquartile range (IQR) for quantitative variables. The Wilcoxon signed-rank test was used to compare preoperative and postoperative quantitative variables. A student-*t*-test was used to compare change in pad use and outcome on the PGI-I scale. Time to ProACT™ failure is distributed in a Kaplan-Meier curve. A binary multivariate logistic regression analysis was conducted using the backward method. The parameters (age, BMI, pre-

operative use of >5 pads per day, time between prostatectomy and implantation of ProACT™, and complications) with $P < 0.05$ on univariate analysis were considered in building the model to investigate the association between these variables and a non-successful outcome.

3. RESULTS

A total of 143 out of 150 patients were included; the median follow up period was 46.0 (IQR 21.0-76.0) months. Seven patients with a sling or AUS in situ were excluded. Patient characteristics are shown in Table 1. The median time between prostatectomy and ProACT™ implantation was 37.0 months (IQR 20.0 – 87.0 months). Twenty-one (14.7%) patients had undergone prior anti-incontinence surgery with bulking agents, AUS, urethral sling, urethrotomy, and/or ProACT™ in various hospitals. At the time the questionnaires were sent 11 patients were deceased. Overall, the median preoperative anamnestic pad use per day was 3.5 (IQR 2.0 – 5.0, $n = 143$). Urinary incontinence was classified as mild in 36 (25.2%), moderate in 57 (39.8%) and severe in 50 (35.0%) patients.

3.1 Continence outcome

After implantation and a median of four balloon volume adjustments daily pad usage had decreased significantly from a median of 3.5 (IQR 2.0-5.0) pads per day preoperatively to a median of 1.0 (IQR 0.0-2.0) pads per day at 6 months and 0.0 (IQR 0.0-2.0) pads per day at 1 year (Table 2). Six months after implantation 72.9% (97/133) patients had ≥50% reduction in daily pad use against preoperative, including 47.4% (63/133) who had become dry (no pad or one security pad per day). After 1 year 50.6% (48/95) patients were dry (no pad or one security pad per day) of the 77.9% (74/95) patients whose daily pad use was reduced with ≥50%. The score on the IPSS quality of life item (IPSS-QOL) had improved significantly from 5.0 (IQR 4.0-5.0) preoperative to 2.0 (IQR 1.0-4.0) 6 months after implantation and 1.0 (IQR 0.0-3.0) 12 months after implantation (Table 2).

TABLE 1. Patient characteristics of the study population presented as number (%) or median (interquartile range). [a] Unless stated otherwise.

Characteristics *n* = 143[a]		
Age, years [IQR]	69.0 [66.0 – 73.0]	
Weight, kg [IQR]	83.0 [78.0 – 89.0]	(*n* = 142)
BMI, kg/m^2 [IQR]	26.1 [24.1 – 28.1]	(*n* = 142)
Type of prostatectomy		
- Retropubic radical prostatectomy	65 (45.5)	
- Laparoscopic radical prostatectomy	33 (23.0)	
- Robot-assisted radical prostatectomy	45 (31.5)	
Previous urological surgery		
- Urethrotomy	9 (6.3)	
- Male sling	2 (1.4)	
- AUS	5 (3.5)	
- Bulking agents	3 (2.1)	
- AUS and urethrotomy	1 (0.7)	
- Male sling and ProACT™ in different clinic	1 (0.7)	
Incontinence severity before		
- mild: 1-2 pads/day	36 (25.2)	
- moderate: 3-4 pads/day	57 (39.8)	
- severe: 5 or more pads/day	50 (35.0)	
ASA score		
- I	27 (18.9)	
- II	95 (66.4)	
- III	21 (14.7)	
Type of anesthesia		
- Spinal	18 (12.6)	
- General	125 (87.4)	
Operating time, minutes [IQR]	69.0 [60.0 – 77.0]	(*n* = 123)
Number of adjustments, *n* [IQR]	4.0 [2.0-6.0]	(*n* = 139)
Volume left balloon, mL [IQR]	4.5 [2.5-7.0]	(*n* = 134)
Volume right balloon, mL [IQR]	4.5 [2.5-7.0]	
Died		
- reason unknown, after follow up	5	
- malignancy	4	
- multi organ failure	1	
- Suicide	1	

TABLE 2. Outcome on daily pad usage, continence, IPSS total, and IPSS QOL, presented as number (%) or median (interquartile range).

	Preoperative	**6 months after implantation**	**1 year after implantation**	**Median 56 [28 -79] months follow up**
	n = 143	*n* = 133	*n* = 95	*n* = 112
Anamnestic pads/day, median [IQR]	3.5 [2.0-5.0]	1.0 [0.0-2.0]	0.0 [0.0-2.0]	1.0 [0.0-2.9]
***P*-value**, (difference from preoperative)[a]	-	<0.001	<0.001	<0.001
		n = 133	*n* = 95	*n* = 112
Postoperative outcome on continence				
- **Successful**, *n* (%)		63 (47)	48 (51)	51 (45)
- **≥50-99% reduction in daily pad use,** *n* (%)		34 (26)	26 (27)	21 (19)
- **Little or no improvement,** *n* (%)		36 (27)	21 (22)	40 (36)
	n = 78	*n* = 107	*n* = 65	
IPSS total, median [IQR]	8.5 [4.8-14.0]	6.0 [3.0-10.0]	5.0 [2.0-11.0]	
***P*-value**, (difference from preoperative)[a]	-	0.38	0.08	
	n = 81	*n* = 106	*n* = 66	
IPSS QOL, median [IQR]	5.0 [4.0-5.0]	2.0 [1.0-4.0]	1.0 [0.0-3.0]	
***P*-value**, (difference from preoperative)[a]	-	<0.001	<0.001	

[a]The Wilcoxon signed-rank test was used to compare preoperative and postoperative results.

3.2 Questionnaire

The questionnaires were sent to 132 patients with a response rate of 120 (90.9%). The median time between the implantation of ProACT™ and the questionnaire was 59.0 (IQR 29.0 – 87.0) months. One hundred and six (88.3%) patients would recommend the ProACT™ to someone else, eight (6.7%) not and six (5.0%) did not answer this question. In eight (6.7%) patients who responded on the questionnaire, the ProACT™ has been removed; in three patients an AUS was implanted; in two patients a male sling was implanted; two patients accepted the incontinence; and one patient was on the waiting list for the ProACT™. One hundred and twelve (93.3%) patients had the ProACT™ in situ and 32 (28.6%) responders had one or more ProACT™ revisions. The daily pad use of the 112 responders with ProACT™ in situ was significantly reduced from 3.0 (IQR 2.0-4.9) to 1.0 (IQR 0.0-2.9) pads per day after a median follow up of 56.0 (IQR 27.5 – 79.0) months ($P < 0.001$, table 2). This corresponds with a 66.7% decrease in pad use. The median outcome on the PGI-I scale in the patients with the device in situ was 2.0 (IQR 1.0-2.0, $n = 111$). Ninety-seven (87.4%) patients reported improvement; 14 (12.6%) no difference or deterioration. The mean difference in pad use before and after the implantation was significantly different in those two groups ($P = 0.03$), namely in the group with improvement on the PGI-I scale mean decrease of 2.5 pad per day (mean pad use pre-operative 3.7) and in the group with no difference or deterioration on the PGI-I scale 0.0 pad per day (mean pad use pre-operative 5.3).

3.3 Intra-operative complications

Seventeen (11.9%) intraoperative perforations of the urethra occurred. In two cases, there was minimal perforation and patients received antibiotics and the transurethral catheter was removed the same day. The other 15 patients were treated with a transurethral catheter from 5 to 7 days.

3.4 Post-operative complications

In Table 3 the short-term (<30 days) post-operative complications and management are summarized. By the Clavien-Dindo classification, three (2.1%) complications were grade IIIb. Two (1.4%) patients had post-operative pain. A total of 129 (90.2%) patients had no complication. On the long term (>30 days), 78 (55.7%) patients had no complication. There were 79 (55.2%) patients without failure of the ProACT™. One or more revisions had been done in 43 (30.1%) patients, mostly because of an unilateral balloon defect (Table 4). Two patients received an AUS after one ProACT™ revision and one patient after two ProACT™ revisions. After balloon failure nine (6.3%) patients accepted the situation. An additional surgery was given to six (4.2%) patients (eg, onabotulinumtoxin-A injected in the bladder wall, sacral neuromodulation, bulking agents). Six (4.2%) patients with

failure of the ProACT™ received a different device after removing the balloons (four patients an AUS and two patients a male sling). The failure-free survival after ProACT™ implantation is shown in a Kaplan-Meier curve (Figure 1).

TABLE 3. Post-operative complications, <30 days, presented as number and graded using the Clavien-Dindo Classification.

	***n* = 143**	**Cause**	**Management**
No complication	129		
Grade I	8	7 acute urinary retention	catheter for a week and prophylactic antibiotics around removing the catheter
		1 intraoperative perforation and scrotal hematoma	catheter for a week and antibiotics
Grade II	3	2 scrotal hematoma and pain	oral pain medication
		1 infection	antibiotics
Grade IIIb	3	1 urethral perforation and hematuria	removed under local anesthetics and new balloons were implanted 2-4 months after removal
		1 infection and intraoperative perforation	
		1 dislocation and pain	

TABLE 4. Reasons of ProACT™ reinterventions, presented in numbers (%).

ProACT reinterventions	**First redo**	**Second redo**	**Third redo**	**Fourth redo**
Defect of the balloon(s)	22 (15.4)	8 (5.6)	1 (0.7)	
Infection	5 (3.5)	1 (0.7)	1 (0.7)	1 (0.7)
Bladder neck perforation	2 (1.4)	2 (1.4)	1 (0.7)	
Erosion	2 (1.4)			1 (0.7)
Persistent incontinence	8 (5.6)			
Migration/dislocation	4 (2.8)	2 (1.4)		
Total	**43 (30.1)**	**13 (9.1)**	**3 (2.1)**	**2 (1.4)**

After a median follow up of 56.0 months univariate logistic analysis showed, intraoperative perforation (OR 13.89, $P = 0.012$), short (OR 8.00, $P = 0.001$) and long term (OR 6.83, $P < 0.001$) complication, and the number of adjustments of the balloons (OR 1.47, $P < 0.001$) were significant parameters. Whereas age ($P = 0.431$), BMI ($P = 0.942$), time between prostatectomy and implantation of ProACT™ ($P = 0.889$), and pre-operative >5 reported pads per day ($P = 0.183$) were not significantly parameters and

were not considered in building the model. Multivariate logistic regression analysis showed short term complications (OR 8.41, $P = 0.004$) and the number of adjustments of the balloons (OR 1.46, $P = 0.002$) were both independently associated with a non-successful outcome.

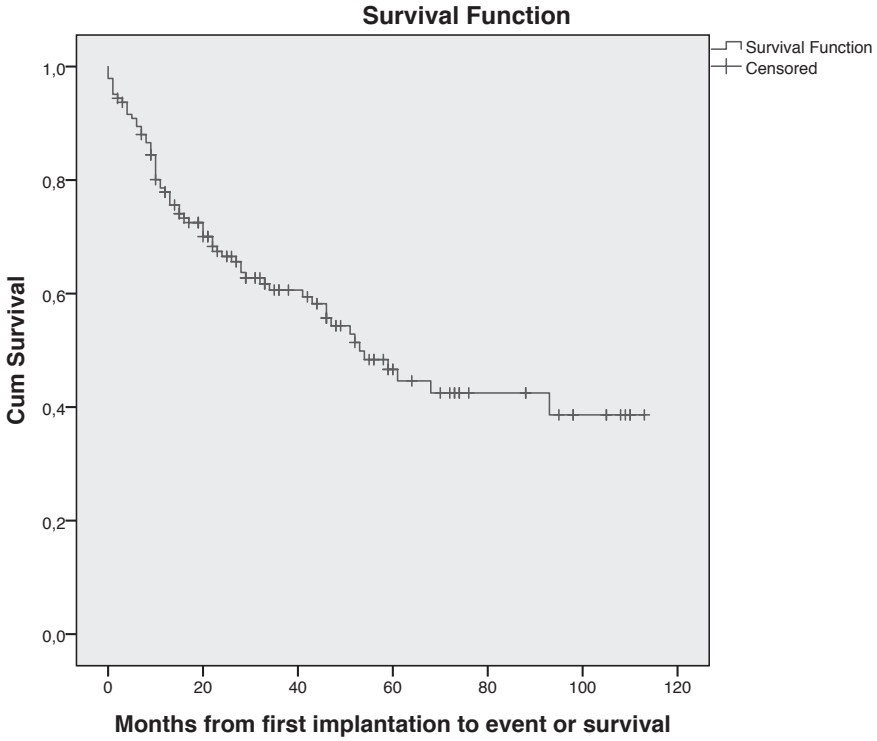

FIGURE 1. Failure free survival after implantation of ProACT™ distributed in a Kaplan-Meier curve.

4. DISCUSSION

The aim of this study was to evaluate our results with the implantation of the ProACT™ device, with a focus on the patients' perception of improvement after implantation. After a median follow up of 56 months, 112 patients with ProACT™ in situ reported a 45% dry rate and a 64% improvement of continence rate. The dry rate in our study is within the range (4.5-66%) reported in studies with comparable follow up.[10-12] Venturino et al[12] defined dry as "no pads" versus "no or one security pad" in our study and the studies of Kjaer et al[10] and Rouprêt et al[11]. Further, the decrease in daily pad use (67%)

in our study is more beneficial than reported in other studies with comparable follow up, ranging from 34% to 65%.[10-12] However, patient baseline characteristics were not comparable with those in other studies.[10-12] Our study population were men with SUI after RP without a history of adjuvant radiotherapy and we did not include patients with SUI after a transurethral resection of the prostate. A recently performed systematic review comparing surgical devices for SUI after RP reported an average dry or one safety pad rates of 66%, 48% and 64% for AUS, male sling, and ProACT™, respectively.[4] Therefore, balloon compression devices like ProACT™ and AUS seem to have similar superior symptom related outcome compared to the male sling, but the AUS was associated with the highest complication rate.[4]

In our study population, revision of ProACT™ was done in 43 (30%) patients. This revision rate is within the range of the literature, ranging from 13% to 73%.[1,10-12] A significant difference was found in the mean number of balloon adjustments between the failure and the failure-free group, 5.4 versus 3.0 adjustments, respectively. This implicates that more tension on the balloon wall results in a higher chance of balloon failure. Another hypothesis could be that patients will become more active with better continence, which gives potentially more traction on the scrotally placed tubes resulting in friction between the balloons and ramus inferior of the pubic bone.

Almost 90% of the patients were satisfied with this treatment, which can be concluded from the scores on the PGI-I scale and the recommendations to others. The median outcome on the PGI-I scale after a median follow up of 56 months was “much better” and 87% perceived improvement. Besides, the change in pad use after the implantation was significantly different between the group with improvement and the group with no difference or deterioration on the PGI-I scale. Experiencing improvement seems to be proportional to improvement on the change in pad use. The PGI-I may be a valuable tool to evaluate a man’s overall appraisal of his condition and his response to surgical treatment for SUI in clinical practice and studies. Since many patients are coming from regions outside the direct vicinity of our hospital, they informed themselves via relatives and/or internet on the possibility of the adjustable continence balloons and asked for referral to our hospital. Consequently, almost all patients choose to be implanted with these balloons initially and not with the alternative options. This could give some bias on the satisfaction. Another possible bias could be the time between the question and the operation. The patient could forget how the situation was precisely before the operation. The validity of the PGI-I in men with SUI has not yet been established. However, a good construct validity of the PGI-I has been established in women with SUI and in men with lower urinary tract symptoms secondary to benign prostatic condition.[13,15]

In contrast to Utomo et al[6] severe pre-operative urinary incontinence (>5 pads per day) and longer duration of PPI in the present study were not independently associated with non-successful treatment outcome. This discrepancy is possibly explained by our longer median follow up (56 vs 9 months) and larger number of patients (112 vs 49). Short term complication and the number of balloon adjustments were significantly associated with a non-successful outcome. The intraoperative perforations were included in the short term complications. The majority of the short term complications were due to an intraoperative perforation. A non-successful outcome after a intraoperative perforation might be the result of the more lateral position of the balloon at the site of the perforation and the necessity for more balloon adjustments to achieve continence. It might be concluded not to place the balloon at the site of perforation in the same surgical session but this necessitates an extra operation and results in financial damage due to loss of the balloon.

Limitations of our study are inherent to the retrospective design. Moreover, the individual learning curve of the surgeon involved might have affected the results. As described by Hübner and Schlarp[8] the treatment outcome can be improved with the learning curve.

Strengths of our study are the large number of patients and the relatively long follow up period. In various cohort and feasibility studies the follow up period ranged from 51 to 58 months and the number of patients from 22 to 128.[10-12] The prospectively sent questionnaire provided patient-determined estimates of their outcome and changes in daily pad use, which can be considered a strength.

The results suggest that ProACT™ is the minimal invasive first line surgical treatment for PPI (without stratification of severity of PPI) before opting for a more invasive treatment, such as male sling or AUS. The balloons can be adjusted in the outpatient clinic, in case of failure the device can be easily removed in the outpatient clinic and another treatment or revision can be considered. Further research is needed, however, to determine outcome predictors. A possible outcome predictor could be the anatomy of the bladder neck post-prostatectomy.

5. CONCLUSION

Our results demonstrate improvement of the continence rate and satisfaction in the majority of patients with SUI after RP without a history of radiotherapy after implantation of adjustable continence balloons. The revision rate should be discussed preoperatively with patients. Future clinical evaluation is, however, necessary to determine outcome predictors.

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CHAPTER 5

Outcome and complications of adjustable continence therapy (ProACT™) in the treatment of urinary incontinence after transurethral resection of the prostate: a multicenter study

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ABSTRACT

Aims: To evaluate the outcome of adjustable continence balloons in the treatment of stress urinary incontinence (SUI) after transurethral resection of the prostate (TURP).

Methods: In two tertiary centers, adjustable continence balloons were implanted in 29 patients with post-TURP SUI between 2007 and 2018. Endpoints of this retrospective multicenter study were patient-reported changes in pad count and complications. Dry was defined as no pad or one security pad.

Results: Preoperative urinary incontinence was mild in 7 (24%), moderate in 12 (41%), and severe in 10 (35%) patients. The median follow-up duration was 21 (interquartile range [IQR] IQR 11-43) months. Within 30 days postoperatively, a Clavien-Dindo grade ≤II complication occurred in 24% of the patients. Reintervention rate was 24%. Six and 12 months after implantation, the International Prostate Symptom Score (IPSS) quality-of-life item improved significantly from 5 (IQR 5-6) preoperatively to 3 (IQR 1-4.5), and 1 (IQR 0-3), respectively. At last visit (median 21 months after implantation), outcome on continence had improved in 76% of the patients, including 45% dry patients. After a median follow-up of 28 months (IQR 13-63, $n = 23$), all but one patient reported improvement on the Patient Global Impression of Improvement (PGI-I) scale. In detail, 10 patients reported "very much better" condition compared to before the implantation, 10 patients "much better", two patients "a little better", and one patient "no change". Daily pad use decreased from three (IQR 2-5) to one (IQR 0-2) pads per day ($P < 0.001$).

Conclusions: This is hitherto the first study reporting results of adjustable continence balloons in the treatment of post-TURP SUI. The therapy was found to be safe and efficient. The majority of our study population reported improvement on their condition and ≥50% reduction in daily pad use.

1. INTRODUCTION

A transurethral resection of the prostate (TURP) is currently the standard surgical procedure in the treatment of a bladder outlet obstruction caused by benign prostate enlargement.[1,2] A rare but unfortunate complication is post-TURP urinary incontinence.[3] Post-TURP urinary incontinence can be due to damage to the sphincter, pre-existing bladder dysfunction, or new onset bladder dysfunction.[3] According to the International Consultation on Incontinence (ICI), the incidence of post-TURP stress urinary incontinence (SUI) is about 1%, irrespective of the TURP techniques used (ie, monopolar, bipolar, or laser).[3]

Urinary incontinence after prostate surgery can significantly alter a person's quality of life.[4,5] In cases of male SUI secondary to sphincter deficiency, conservative treatment may be tried for periods up to 6 to 12 months in advance of a surgical treatment.[3-5] When conservative treatment fails, several surgical implants are available, such as artificial urinary sphincter, male sling, and adjustable continence balloons.[3-5] The latter device consists of two periurethrally placed balloons (ProACT™) whose volumes can be adjusted to achieve the optimal balance between voiding pressure and continence.[6] Reported long-term dry rates (no pad or one security pad) range from 45% to 66% with a follow up of 56 to 58 months.[7-9] The majority or all patients included in these studies were treated for SUI after radical prostatectomy. Patients with post-TURP SUI are a different population in view of a different mechanism of injury. Usually, it is damage to the proximal part of the external striated urethral sphincter distal to the verumontanum.[4]

The aim of this retrospective multicenter study was to evaluate the efficacy of adjusted continence balloons in patients with post-TURP SUI. Efficacy and safety were evaluated in terms of achieving continence, changes in pads use, complications, re-interventions and patient-reported estimates of improvement assessed with the Patient Global Impression of Improvement (PGI-I) scale.

2. PATIENTS AND METHODS

We retrospectively evaluated data prospectively collected from all patients who had the ProACT™ (Uromedica, Inc., MN) device implanted as surgical treatment of post-TURP SUI after May 2007 in two tertiary centers: Erasmus University Medical Center in Rotterdam, the Netherlands and Policlinico Tor Vergata in Rome, Italy. Conservative treatment with pelvic floor exercises had failed in all patients. Urethrocystoscopy and urodynamic study were performed to rule out urethral strictures and to evaluate the bladder function.

Exclusion criteria were a history of radiotherapy, neurogenic bladder dysfunction, and a male sling or an artificial urinary sphincter (AUS) in situ. The local ethics committee of Erasmus University Medical Center in Rotterdam approved this study (MEC-2017-05, MEC-2018-1287). The Comitato Etico Policlinico Tor Vergata in Rome gave a general permission to anonymously collect data for scientific purposes.

Preoperative assessment included medical history, anamnestic daily pad count, voiding diary, and International Prostate Symptom Score (IPSS). The preoperative severity of urinary incontinence was determined by the anamnestic daily pad count, classified as mild (1-2 pads), moderate (3-4 pads), or severe (≥5 pads). In each institution, one experienced surgeon had implanted the adjustable continence balloons using the technique described by Hübner and Schlarp[6]. In brief, two ProACT™ balloons were implanted via two incisions in the perineum, at either side of the bladder neck. Most of the patients were under general anesthesia and some under spinal anesthesia during the procedure. Intravenous cefazolin and metronidazole were given perioperatively as antibiotic prophylaxis. After removal of the transurethral catheter and a successful voiding trial, patients were discharged from hospital on the day of surgery or the day after. Within a period of six months after the implantation, the balloon volume was adjusted at the outpatient clinic by needle puncture of the subcutaneous port in the scrotum. Postoperative assessment included anamnestic daily pad count, IPSS, and complications.

All patients in Rotterdam received an information letter, a three-item questionnaire and a return envelope by post. In Rome, those three questions were asked during last scheduled outpatient visit. The three questions asked were:

1. "Would you recommend adjustable continence balloons to someone else?" to be answered by yes or no.
2. Which number describes how your condition is now compared to before the adjustable continence balloons: 1. "very much better", 2. "much better", 3. "a little better", 4. "no change", 5. "a little worse", 6. "much worse", 7. "very much worse" (PGI-I scale).
3. How many pads do you use daily?

Other relevant patient characteristics were retrospectively retrieved from the medical charts. Treatment outcome on continence was assessed by the change in preoperative and postoperative anamnestic daily pad use. The definition of "dry" was no pad or a single security pad per day. "Improvement" was defined as a daily pad reduction of ≥50% compared to the preoperative situation. "Little/no improvement" was defined as

no or less than 50% reduction of daily pad use compared to preoperative. Perception of improvement on condition was assessed with the PGI-I (7-points) scale; a lower score corresponds with a better condition. Complications within 30 days were classified by the Clavien-Dindo Classification of Surgical Complications.[10] Failure of the interventions was defined as explantation with or without revision of adjustable continence balloons, or as an additional surgical procedure because of persistent incontinence, or as acceptance of the situation with persistent incontinence.

Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY). Descriptive statistics are presented as percentages for qualitative variables and median and interquartile range (IQR) for quantitative variables. The Wilcoxon signed-rank test was used to compare preoperative and postoperative quantitative variables. Pearson's chi-squared test was used to compare categories. Time to adjustable continence balloons failure is distributed in a Kaplan-Meier curve. A two-sided *P*-value < 0.05 was considered statistically significant.

3. RESULTS

Twenty-nine out of 31 eligible patients were included; 26 patients in Rotterdam and five in Rome. Reason for exclusion in two patients was a non-functional male sling in situ, both patients were included in Rotterdam. Urinary incontinence was classified as mild in 7 (24.1%), moderate in 12 (41.4%), and severe in 10 (34.5%) patients. Median preoperative anamnestic pad use per day was 3.5 (IQR 2.3-5.3). The median time between TURP and balloon implantation was 2.2 (IQR 1.3-3.6) years. TURP had been performed because of lower urinary tract symptoms secondary to benign prostate enlargement. Two patients had prior anti-incontinence surgery with bulking agents. Preoperative assessment of the external urethral sphincter with urethrocystoscopy showed normal findings in 15 (51.7%) patients; three out of 15 patients had severe incontinence. The sphincter remained open in 14 (48.3%) patients; severe incontinence was seen in seven out of 14 patients. More severe incontinence was seen in patients with abnormal urethrocystoscopy findings (50.0% versus 20.0%, $P = 0.09$). Patient characteristics are shown in Table 1.

TABLE 1. Patient and clinical characteristics presented as number (%) or median (interquartile range).

Characteristics *n* = 29[a]		
Age, years	70.5 (66.7-77.7)	
Weight, kg	82.0 (75.5-94.0)	
BMI, kg/m2	27.5 (24.8-30.0)	
Type of TURP		
- Monopolar or bipolar	24 (82.8)	
- Laser	5 (17.2)	
ASA score		
- I	3 (10.3)	
- II	18 (62.1)	
- III	8 (27.6)	
Type of anesthesia		
- General	20 (69.0)	
- Spinal	9 (31.0)	
Operating time, minutes	33.0 (26.8-38.5)	*n* = 28
Number of adjustments	5.0 (2.0-5.5)	
Volume left balloon, mL	5.0 (2.0-6.5)	
Volume right balloon, mL	5.0 (2.0-6.5)	
Complications within 30 days		
- No complication	22 (75.9%)	
- Clavien-Dindo grade I	6 (20.7%)	
- Clavien-Dindo grade II	1 (3.4%)	

[a]Unless stated otherwise

3.1 Continence outcome

The median number of balloon volume adjustments after implantation was five (Table 1). Six months after implantation, the median pad use per day was 1.0 (IQR 1.0-1.9); after 1 year it was 1.0 (IQR 0.0-2.5). The IPSS quality of life score had improved significantly from preoperative 5.0 (IQR 5.0-6.0) to 3.0 (IQR 1.0-4.5) 6 months after implantation and to 1.0 (IQR 0.0-3.0) 1 year after implantation. The median time between implantation and last outpatient visit was 20.9 (IQR 10.5-43.4) months. The daily pad use reported at the last visit was 1.0 (IQR 0.0-2.0). At the last visit, 75.8% (22 of 29) of the patients reported ≥50% reduction in daily pad use against the preoperative, including 44.8% (13 of 29) who had become dry. The seven patients with preoperative mild incontinence were all dry at last visit. In the 12 patients with preoperative moderate incontinence the outcome at last visit was: dry in four, improved in three, and little or no improvement in five patients. Two out of ten patients with preoperative severe incontinence were dry, six patients were improved and two patients had little or no improvement. In the

TABLE 2. The outcome on daily pad usage, continence, IPSS total, and IPSS QoL, presented as number (%) or median (interquartile range).

	Preoperative	**6 months after implantation**	**1 year after implantation**	**Last visit median FU 20.9 (10.5-43.4) months**
	n = 29	*n* = 28	*n* = 21	*n* = 29
Anamnestic pads/day, median (IQR)	3.5 (2.3-5.3)	1.0 (1.0-1.9)	1.0 (0.0-2.5)	1.0 (0.0-2.0)
***P*-value,** (difference from preoperative)[a]	-	<0.001	0.004	<0.001
		n = 28	*n* = 21	*n* = 29
Postoperative outcome on continence				
- Dry, *n* (%)		9 (32.1)	6 (28.6)	13 (44.8)
- ≥50-99% reduction in daily pad use, *n* (%)		12 (42.9)	7 (33.3)	9 (31.0)
- Little or no improvement, *n* (%)		7 (25.0)	8 (38.1)	7 (24.1)
	n = 20	*n* = 25	*n* = 15	
IPSS total, median (IQR)	13.0 (10.3-16.0)	7.0 (4.0-14.5)	6.0 (3.0-10.0)	
***P*-value,** (difference from preoperative)[a]	-	0.001	0.007	
	n = 20	*n* = 25	*n* = 15	
IPSS QoL, median (IQR)	5.0 (5.0-6.0)	3.0 (1.0-4.5)	1 (0.0-3.0)	
***P*-value,** (difference from preoperative)[a]	-	0.001	0.005	

FU, follow-up; IPSS, International Prostate Symptom Score; IQR, interquartile range; QoL, quality of life.
[a]The Wilcoxon signed-rank test was used to compare preoperative and postoperative results.

whole study population, one patient needed a single re-adjustment of the balloons (0.5 mL) more than 5 years after the last adjustment. The other patients had no additional adjustments. Table 2 provides details on daily pad use, postoperative outcome on continence, and IPSS.

3.2 Questionnaire

After a median follow up of 28.1 (IQR 12.8-62.9) months, 23 patients had completed the three-item questionnaire (response rate 79.0%). Two patients did not respond and four patients (minimal 4 months after the end of follow-up) had died at the time the questionnaire was sent. The reason of death was not related to the surgical procedure. Results are presented in Table 3. All patients would recommend adjustable continence balloons to someone else. Daily pad use improved significantly from 3.0 (IQR 2.0-5.0) to 1.0 (IQR 0.0-2.0) pads per day ($P < 0.001$). Outcome on continence had improved in 15 (65.2%) of the patients, including six (26.1%) dry patients. Twenty-two (95.7%) patients reported improvement on the PGI-I scale. In detail, the condition now compared with the condition before the adjustable continence balloons was reported "very much better" in 10 (43.5%) patients, "much better" in 10 (43.5%) patients, "a little better" in two (8.7%) patients, and "no change" in one (4.3%) patient.

3.3 Complications

In one patient an intraoperative complication occurred, that is, a perforation of the urethra during positioning of the right balloon. The balloon was still placed just lateral to the perforation. In contrast to the other patients, this patient was discharged from hospital with a transurethral catheter. Five days postoperatively, prophylactic antibiotics were started and the transurethral catheter was removed. At 6 months and 12 months postoperative, his pad use was improved from 6 pads per day preoperative to 2.5 and 1.5 pads per day, respectively.

Twenty-two (75.9%) patients were complication-free within 30 days postoperatively. The remaining seven patients had an acute urinary retention. The balloon volume was reduced in one patient, which resulted in a successful voiding trial. In the other six patients, the transurethral catheter was replaced and removed at day 5 or 7 with oral antibiotics started at approximately the removal time. In one of these patients, epididymitis was treated with oral antibiotics 3 days after removal of the transurethral catheter.

TABLE 3. The outcome on three-item questionnaire, presented as number (%) or median (interquartile range).

Results of prospective follow-up	
Postoperative follow-up in months	28.1 (12.8 -62.9)
Recommend balloons to someone else?	
Yes	23 (100)
No	-
PGI-I scale	
1. very much better	10 (43.5)
2. much better	10 (43.5)
3. a little better	2 (8.7)
4. no change	1 (4.3)
5. a little worse	-
6. much worse	-
7. very much worse	-
Daily pad use	
Preoperative	3.0 (2.0-5.0)
Postoperative	1.0 (0.0-2.0)
Postoperative outcome on continence	
Dry	6 (26.1)
50-99% reduction in daily pad use	9 (39.1)
Little or no improvement	8 (34.8)

Failure of the intervention was seen in nine (31.0%) patients after a median follow-up of 18.1 (IQR 8.4-21.6) months. The failure-free survival curve is presented in Figure 1. Four patients had unchanged urinary incontinence of whom two accepted the situation. The other two patients had additional surgery with bulking agents. At last visit, outcome on continence was improved in both patients. One or more replacements were performed in five patients; in two on account of malposition of the balloon and in three on account of a defective of the balloon. A second replacement was necessary in two patients because of erosion of one of the balloons through the urethra. The outcome on continence at last visit was in three patients little or no improvement, and in two patients improvement, including one dry patient. Preoperative severe incontinence was seen in six (66.7%) of the nine patients in whom the intervention had failed versus four (20.0%) of the 20 patients in whom the intervention was successful ($P = 0.014$).

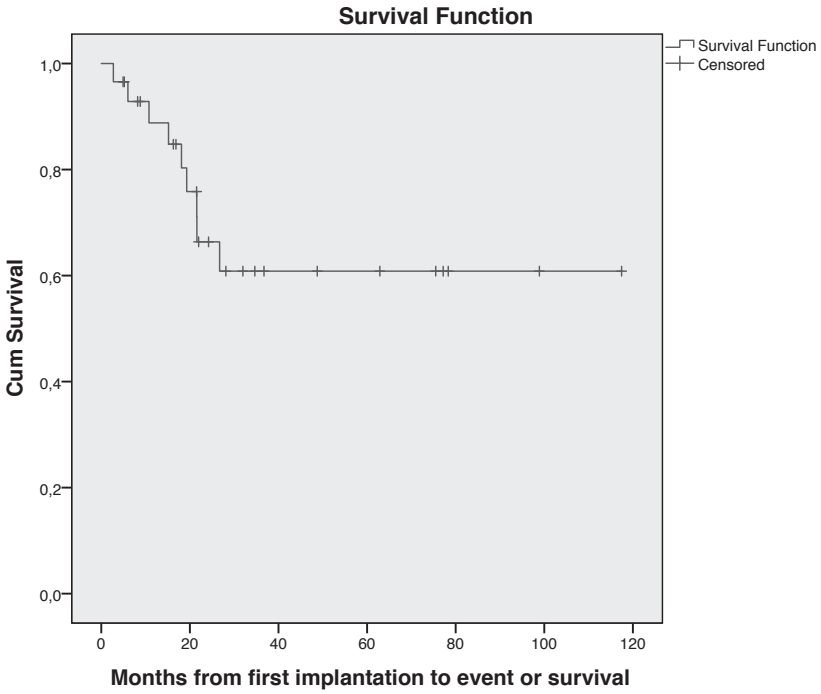

FIGURE 1. Failure free survival after implantation of balloons distributed in a Kaplan-Meier curve.

4. DISCUSSION

The aim of this study was to evaluate the efficacy of adjustable continence balloons in the treatment of post-TURP SUI. After a median follow-up of 21 months, two-thirds (22 of 29) of the patients reported to use fewer pads daily, and 13 of the 29 patients were even dry. All but one patient reported improvement on the PGI-I scale. Within 30 days postoperatively, a Clavien-Dindo grade ≤II complication had occurred in 24% of the patients.

Male postsurgical SUI can be caused by direct surgical injury to the external urethral sphincter or its innervation, though this may coexist with bladder dysfunction.[4,5] Post-TURP SUI is most likely the result of damage to the proximal part of the external urethral sphincter distal to the verumontanum.[4] Several additional mechanisms of sphincteric injury after radical prostatectomy have been suggested, like: ischemia and immobilization by scar, atrophy due to incomplete recovery, direct pudendal nerve

injury or shortening of urethra below critical functional length.[11] Regarding the different etiologies of male SUI, presumably this can have influence on the outcome of a surgical treatment.

A recent systematic review addressed functional outcome and complications in the treatment of male postsurgical SUI with adjustable continence balloons.[12] Eleven studies were included, of which six studies included as well patients with post-TURP SUI in the study population. In one of the excluded studies (because of a patient population of < 20) post-TURP SUI patients were included as well. An overview of those seven studies with post-TURP SUI patients is given in Table 4 [6-8,13-16]. Nevertheless, none of these studies differentiated outcome after radical prostatectomy and post-TURP. Reported dry rates varied between 4.5% and 67% and reintervention rates varied between 14% and 46% (Table 4). The dry rate (45%) at last outpatient visit, and reintervention rate (24%) found in the present study fall within the respective ranges. Additionally, the previously published results of adjustable continence balloons in patients with SUI postradical prostatectomy implanted by one of the surgeons of this study[9] were added to Table 4 to compare with the present study. Overall, results in literature are slightly similar, but important to note, besides the etiology, the size, and duration of follow-up of study populations differ. In short, studies are hard to compare because the etiology of SUI, history of adjuvant radiotherapy, duration of follow-up, different centers and surgeons, and definitions of outcome used in the literature are heterogeneous. Our study is hitherto the first reporting results of adjustable continence balloons in in the treatment of post-TURP SUI.

The median postoperative daily pad use remains stable during follow-up (see Table 2 and Table 3). Remarkably, we observed a decline of dry rate at the time the PGI-I scale was answered. The efficacy of the balloons could have been reduced. Another possible explanation for this decline in dry rate could be that continent patients will become much more active in time compared than they were preoperatively which can result in more "stress" and a decline in dryness. Furthermore, not all patients responded or could response and, therefore, the decline could also partly be explained by selection bias. Despite the decline of dry rate, the majority experienced improvement on PGI-I.

If conservative treatment fails, the standard in surgical management of male SUI is AUS.[4,17,18] However, alternatives to AUS, such as male sling and adjustable continence devices, are available. These devices do not require manual manipulation to void. Implantation of adjustable continence balloons is less invasive and has the advantages of adjusting the volume or removing the balloons in the outpatient setting. Besides, opting

TABLE 4. Overview of the current literature on studies which included adjusted balloon therapy in post-TURP stress urinary incontinence.

Study	Number of patients	Post-TURP patients, *n* (%)	Type of TURP specified, *n*	Post-TURP results reported separately	History of radiotherapy, *n*(%)	Median/ mean months of FU	Definition of dry	Dry, *n* (%)	≥50-99% improvement on pads/day, *n* (%)	Reintervention rate, *n* (%)	Balloon reimplantation rate, *n* (%)
Hübner et al[6]	117	6 (5)	6 TURP	NR	2 (2)	13	No or one security pad	78 (67)	NR	54 (46)	54 (46)
Kocjancic et al[13]	64	3 (5)	3 TURP, including HIFU (*n* = ?)	NR	11 (17)	20	No or one security pad	43 (67)	10 (15)	11 (17)	10 (16)
Gilling et al[14]	37	7 (19)	7 Laser TURP	NR	4 (11)	24	No pads	20 (62)	NR	5 (14)	1 (3)
Giammò et al[15]	18	6 (33)	6 TURP	NR	2 (11)	18	No or one security pad	NR	NR	7 (39)	7 (39)
Roûpret et al[7]	128	8 (6)	8 TURP	NR	30 (23)	56	No or one security pad	85 (66)	NR	23 (18)	17 (13)
Kjaer et al[8]	114	38 (33)	29 TURP 2 Laser TURP 7 palliative TURP	NR	4 (4)	58	0-1 pad/day or daily leakage <8 gram	46 (50)	26 (30)	31 (27)	31 (27)
Venturino et al[16]	22	4 (18)	4 TURP	NR	3 (14)	57	No pads	1 (4.5)	NR	24 procedures	16 (73)
Noordhoff et al[9]	143	0 (0)	-	Only post-RP patients	none	56	No or one security pad	51 (45)	21 (19)	55 (38)	43 (30)
Current study	29	29 (100)	24 TURP 5 Laser TURP	Only post-TURP patients	none	21	No or one security pad	13 (45)	9 (31)	7 (24)	5 (17)

FU, follow-up; HIFU, high-intensity focused ultrasound; RP, radical prostatectomy; NR, not reported; TURP, transurethral resection of the prostate

for more invasive procedures is still possible after removal. The working mechanism of adjustable continence balloons with a successful outcome is contributed by an increase in urethral resistance and increased maximum urethral closure pressure.[19,20]

The ICI reviewed the literature with results of AUS in the treatment of male SUI. Most of the studies included men with post-prostatectomy incontinence related to benign and malignant disease. Success rates range from 59% to 90%, defined by no or 1 pad per day, with a follow-up ranging from 1 to 7.7 years.[3,21] To our knowledge, studies with results of AUS in exclusively post-TURP SUI patients are missing.

Regarding the male sling in the treatment of post-TURP SUI, a few studies are published. Recently a systematic review was published which identified 23 post-TURP patients described in six studies who had undergone a male sling. A successful outcome was described in 78% of the patients with divergent definitions of success (total continence, <2 gram loss of urine, ≥50% pad reduction, subjective improvement in continence).[22] Another study (not included in the above review), reported results of 15 post-TURP patients treated with a male sling with a median follow-up of 70 months.[23] Outcome on continence after implantation of the male sling was improved with a ≥50% pad reduction in 60% of the patients, including 47% dry patients.[23]

It would be interesting to perform trials, preferably randomized, comparing adjustable continence balloons in the treatment of male SUI with other devices, such as male sling or AUS. To prevent mixed patient populations, future studies should differentiate between patients who have post-radical prostatectomy SUI and those who have post-TURP SUI. Besides, future research to define outcome predictors of adjustable continence balloons could be helpful in clinical practice.

Strengths of our study are the multicenter design and the specific study population. The etiology of the SUI was in all patients post-TURP SUI. These patients are a different population with a different mechanism of injury compared to patients with postradical prostatectomy SUI. Both tertiary centers have around one decade of experience in this type of surgery (10-15 procedures/year in Rome and 25 procedures/year in Rotterdam). Still, the study population was relatively small which hindered defining outcome predictors. Another limitation is inherent to the retrospective design of our study. For example, due to the retrospective design, we used the IPSS in the evaluation of the adjustable continence balloons. The IPSS is widely used in our clinical practice and this data was available. This measure focuses on lower urinary tract symptoms, the IPSS total score and IPSS quality of life item improved significantly after implantation. For this patient population a condition-specific questionnaire would be more interesting, such

as the Urogenital Distress Inventory (UDI-6)[24], or the Incontinence Impact Questionnaire (IIQ-7)[24], or the International Consultation on Incontinence Questionnaire (ICIQ)[25]. However, the use of these questionnaires is not widely spread and the minimal critical values have not been established.

5. CONCLUSION

Currently little is known about the efficacy of adjustable continence balloons in the treatment of post-TURP SUI. Adjustable continence balloons seem to be safe and efficient in the treatment of post-TURP SUI. The majority of our study population experienced improvement on their condition and needed fewer pads than before the implantation of adjustable continence balloons. Future research is needed to compare different devices and determine outcome predictors.

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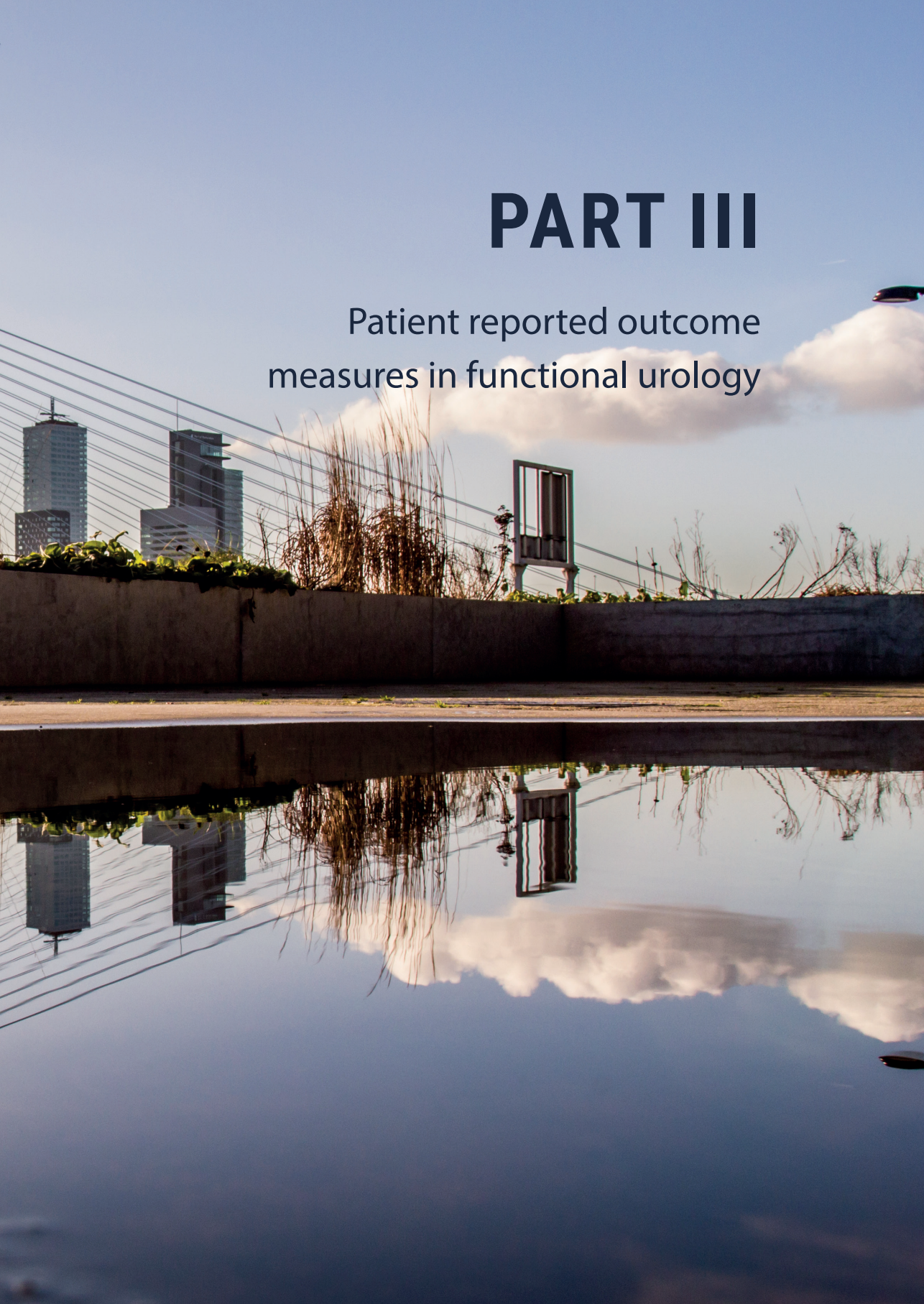

PART III

Patient reported outcome measures in functional urology

CHAPTER 6

The Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-15): validation of the Dutch version in patients with multiple sclerosis and spinal cord injury

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ABSTRACT

Aims: The Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-15) evaluates symptoms of sexual dysfunction in patients with multiple sclerosis (MS). The objective of this study was to provide and validate a Dutch version of the MSISQ-15 in patients with neurological disease such as MS and spinal cord injury (SCI).

Methods: The linguistic validation process of the original English MSISQ-15 into Dutch was performed according to standardized guidelines. Sexually active patients with MS or spinal cord disorders, including SCI and cauda equine syndrome, who visited a tertiary urology center or a rehabilitation center completed the MSISQ-15, Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) in women, or International Index of Erectile Function (IIEF-15) in men at baseline (test) and 2 weeks later (retest). A reference group recruited from a general medical practice completed the questionnaires once. Data were analyzed for measurement properties.

Results: Fifty-three patients with MS, 49 patients with spinal cord disorder, and 50 references were included. Content validity was adequate. Internal consistency (Cronbach's alpha >0.8) and reproducibility (intraclass correlation coefficient >0.8) of the MSISQ-15 were excellent. Patients' MSISQ-15 scores were correlated with severity of symptoms of sexual dysfunction measured by PISQ-12 or IIEF-15 and confirmed positive rating for criterion validity. MSISQ-15 scores in patients were higher than in references (on a scale of 15-75: 38.9 ± 11.4 vs. 21.1 ± 5.4; P <0.001), indicating good construct validity.

Conclusions: The Dutch MSISQ-15 is a reliable and valid measure to evaluate symptoms of sexual dysfunction in patients with MS or with SCI.

1. INTRODUCTION

Living with neurological diseases such as multiple sclerosis (MS) or spinal cord injury (SCI) might have significant consequences for a person's sexual function and quality of life.[1,2] Sexual function can be assessed with patient-reported outcome (PRO) measures, usually a questionnaire. This also allows evaluating change over time.[3]

The Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ) evaluates symptoms of sexual dysfunction (SD) in MS patients, divided in three dimensions. Categorized as primary SD are symptoms as a result of neurologic changes that directly influence sexual function, such as impaired genital sensation, erectile dysfunction, orgasm dysfunction, decreased vaginal lubrication, and loss or reduction of libido. Secondary SD includes symptoms that arise from MS and indirectly influence sexual function, such as muscle tightness, spasticity, bladder and bowel dysfunction, pain, or discomfort in non-genital areas of the body. Tertiary SD refers to the psychological, emotional, social, and cultural aspects of MS that impact sexual function.[4,5] The original version of the MSISQ was in English and consisted of 19 items and has been translated and validated in the Persian[6] and Portuguese languages[7]. A re-evaluation in a larger English cohort resulted in a validated 15 item version.[5]

At this moment, no validated Dutch PRO measure is available to assess SD in patients with a neurological disease. Although the MSISQ-15 was developed for patients with MS, the similarity between the SD symptoms of patients with MS and those with SCI, as well as the similarity in treatment, suggests that the instrument might work well in both populations. This study is designed to provide a validated Dutch version of the MSISQ-15 in patients with neurological diseases.

2. MATERIALS AND METHODS

This prospective validation study was approved by the Institutional Ethics Committee (MEC-2016-370) and conducted at a tertiary urology center and at a rehabilitation center.

2.1. Study populations and study design

2.1.1 Patient group

Adults with MS or SCI or cauda equina syndrome were eligible for inclusion if they spoke Dutch fluently. Exclusion criteria consisted of dementia, mental retardation, active malignant tumors, and no sexual activity during the last 6 months.

All potential eligible patients were informed about the study and invited to participate by the treating physician during a regular outpatient visit between July 2016 and January 2018. After written informed consent patients were asked to complete the questionnaires during the inclusion visit (test) and two weeks later at home (retest). Clinical characteristics of included patients were retrieved from their medical files.

2.1.2 Reference group

The reference group was invited from one general practitioner's practice in January and February 2017. Exclusion criteria consisted of Dutch language difficulties, neuro-urological dysfunction, dementia, mental retardation, and no sexual activity during the last 6 months. Since patients visiting the general practitioner might have less severe health issues, we considered these patients as proper reference group. They provided written informed consent and completed the questionnaires once.

2.2. Questionnaires

The questionnaire set consisted of the MSISQ-15, the EQ visual-analogue scale (EQ-VAS), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12), and International Index of Erectile Function (IIEF-15).

- The MSISQ-15 is a self-report measure that evaluates the influence of MS symptoms on sexual activity and satisfaction over the preceding 6 months. It is a valid and reliable short version of the MSISQ-19 and consists of 15 items. The MSISQ-15 is divided in three dimensions to allow focus on the specific domain of sexual concerns; primary SD (items 8, 12, 13, 14, 15) secondary SD (items 1, 2, 3, 4, 5) and tertiary SD (items 6, 7, 9, 10, 11). Each item is rated on a five-point Liker scale ranging from 0 (never) to 5 (always). The total score is the sum of the fifteen items. The maximum total score is 75; the higher the score the greater the impact of SD on patients' lives.[5]
- The PISQ-12 evaluates sexual function in heterosexual women who suffer from urinary incontinence and/or pelvic organ prolapse; it was not specifically designed for neuro-urological patients. It is a valid and reliable short-form of the PISQ-31, including 12 items.[8] The PISQ-12 is recently translated into Dutch and showed good reliability and validity.[9] Alteration of item 12 during the Dutch PISQ-12 validation study resulted in suboptimal answer options. Without item 12 the Dutch version was still found to be valid and reliable. We used the Dutch PISQ-12 without item 12. Responses are graded on a five-point Likert scale, ranging from 0 (always) to 4 (never). Items 1-4 are reversely scored. The maximum score is 44; higher scores indicate better sexual function.[9]

- The IIEF-15 is a 15-item self-administered questionnaire for the assessment of male sexual function, not specifically for neuro-urological patients. The IIEF-15 addresses five relevant domains of male sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. Linguistic validation of the Dutch IIEF-15 was conducted by the MAPI research Institute in Lyon, France. Responses are graded on a scale for 0 to 5. The maximum score is 75; higher scores indicate better sexual function.[10]
- The EQ-VAS is part of the European Quality of Life-5 Dimensions questionnaire. The patient can indicate the health state on the EQ-VAS, from 0 "the worst health you can imagine" to 100 "the best health you can imagine".

2.3. Linguistic validation

The linguistic validation process of the original MSISQ-15 into the Dutch language was performed according to standardized guidelines.[11] Three professional translators with Dutch as native language separately forward-translated the English MSISQ-15. Differences were discussed with the translators, two urologists (BB and JS), and the primary investigator (TN). Some minor textual changes were made without changing the content, resulting in the final version (see supplementary material), which was then backward-translated by a professional translator with English as native language. The content validity of the Dutch version was evaluated in face-to-face interviews with 20 patients.[12] Patients were asked to complete the questionnaire. Afterwards, the content and wording of the questions were discussed.

2.4. Measurement properties

The following measurement properties were used to validate the questionnaire:

2.4.1. Content validity

The content validity examines the extent to which the items of the questionnaire measure the concepts of interest in the target population. Researchers subjectively assessed the correspondence between the questionnaire items and the clinical symptoms. During the linguistic validation, content validity was assessed from interviews with patients.[12]

2.4.2. Internal consistency

The internal consistency is the correlation between the different items in the questionnaire and demonstrates if the items measure the same underlying construct. A Cronbach's alpha was calculated for the total score and three domains of the MSISQ-15. A Cronbach's alpha between 0.70 and 0.95 was considered to reflect adequate internal consistency.[12]

2.4.3. Reproducibility

The reproducibility is the degree to which scores on a questionnaire are corresponding in repeated measurements in stable persons. This was determined by reliability and agreement. The degree to which patients can be differentiated from each other, despite the measurement error, reflects the reliability. The reliability was calculated using the intraclass correlation coefficient (ICC) for agreement, where ICC scores over 0.70 are acceptable.[12,13] The agreement concerns the measurement error, that is, the similarity in scores rated on separate occasions. Differences within the limits of agreement (LOA) can be interpreted as measurement error. The LOA were calculated as the mean change in scores of repeated measurements ±1.96 x standard deviation of the changes.[13,14]

2.4.4. Criterion validity

The extent to which questionnaire scores relate to a gold standard refers to the criterion validity.[12] For the MSISQ-15 no perfect gold standard exists. In the absence of a gold standard the Dutch PISQ-12 and the Dutch IIEF-15 were used for women and men, respectively. Pearson's correlation coefficient was determined (range -1 to 1); when values are close to the extremes indicate either a more negative or positive correlation.[12]

2.4.5. Construct validity

The construct validity refers to the extent to which hypotheses about the scores of the questionnaire relate to other measures. Construct validity is considered adequate when at least 75% of the results of the predefined hypotheses are in accordance.[12]

The predefined hypotheses were:

1. The reference group will have lower MSISQ-15 scores than the patient group.
2. Female patients with lower PISQ-12 scores will have higher MSISQ-15 scores.
3. Male patients with lower IIEF-15 scores will have higher MSISQ-15 scores.
4. Patients who score higher on the EQ-VAS will have lower MSISQ-15 scores.

2.4.6. Floor and ceiling effects

If more than 15% of the respondents would achieve the lowest or highest possible score, floor or ceiling effects are considered.[12] The floor and ceiling effects were assessed for the total and domain scores at baseline in the patient and reference groups.

2.5. Statistical methods

Based on the guidelines for validation of questionnaires[12], we aimed at a sample size of 50 MS patients, 50 SCI patients, and 50 control persons. Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY). Continuous data are

presented as mean and standard deviation. Categorical data are presented as counts and percentages. Differences between the patient and reference groups or within the patient group, were tested with the Student's *t*-tests for continuous variables and chi-squared tests for categorical variables. Statistical significance was defined as *P*-value <0.05.

3. RESULTS

A total of 106 patients were included in the study. Three patients were excluded from the analysis because they did not return the second questionnaire. One patient did not fully complete the questionnaires and was excluded. Of the 102 included patients who completed both questionnaires, 49 were female and 53 male. Fifty-three patients had MS, of whom 36 (68%) relapsing-remitting MS, 6 (11%) primary progressive MS, 8 (15%) secondary progressive MS, and of 3 (6%) the type of MS was unknown. Forty-three patients had an SCI and six a cauda equina syndrome. The SCI patients were classified by the American Spinal Injury Association (ASIA) impairment scale[15] as follows: 21 (49%) patients ASIA A, 7 (16%) patients as ASIA B, 4 (9%) patients as ASIA C, 8 (19%) patients ASIA D, 1 (2%) patient ASIA E, and in 2 (5%) patients the grade was unknown. The level of SCI was cervical in 13 (30%), thoracic in 26 (61%), and lumbar in 4 (9%). The reference group consisted of 50 adults, of whom 29 were female and 21 male. Table 1 shows the characteristics of the patient and reference groups.

3.1. Content validity

During the linguistic validation process 12 MS and 8 SCI patients judged the content validity to be adequate. The majority confirmed the importance of all questions to assess the broad range of problems in sexual function with their neurological condition. Further, they found the Dutch version clear, understandable, and easy to complete. No adjustments were necessary.

TABLE 1. Demographic and clinical characteristics presented as mean ± standard deviation or numbers (%)

	MS *n* = 53[a]	SCI *n* = 49[a]	*P*-value	Patient group *n* = 102[a]	Reference group *n* = 50[a]	*P*-value
Age, yrs	46.0 ± 10.1	41.3 ± 11.9	0.034[a]	43.7 ± 11.2	40.4 ± 15.2	0.135[b]
Gender						
- Male	12 (22.6)	41 (83.7)	<0.001[c]	53 (52.0)	21 (42.0)	0.248[c]
- Female	41 (77.4)	8 (16.3)		49 (48.0)	29 (58.0)	
Time since diagnosis of neurogenic disease, yrs	10.1 ± 7.5	13.1 ± 11.7	0.125[b]	11.5 ± 9.8	-	-
Mobility						
- Fully ambulatory	17 (32.1)	8 (16.3)	<0.001[b]	25 (24.5)	-	-
- Limited walking	31 (58.5)	9 (18.4)		40 (39.2)		
- Weelchair bound	5 (9.4)	32 (65.3)		37 (36.3)		
MSISQ-15 scores baseline						
- Total score	36.91 ± 12.15	41.04 ± 10.27	0.067[b]	38.89 ± 11.42	21.14 ± 5.39	<0.001[b]
- Primary domain	13.87 ± 4.67	16.39 ± 3.81	0.004[b]	15.08 ± 4.44	8.14 ± 2.93	<0.001[b]
- Secondary domain	12.02 ± 4.44	12.08 ± 4.89	0.946[b]	12.05 ± 4.64	6.84 ± 2.67	<0.001[b]
- Tertiary domain	11.02 ± 5.24	12.57 ± 5.04	0.131[b]	11.77 ± 5.18	6.16 ± 1.22	<0.001[b]
PISQ-12 scores baseline	34.36 ± 4.79 *n* = 41	27.00 ± 3.86 *n* = 8	<0.001[b]	33.16 ± 5.37 *n* = 49	36.17 ± 4.96 *n* = 29	0.016[b]
IIEF-15 scores baseline	37.00 ± 21.69 *n* = 12	41.04 ± 16.83 *n* = 41	0.497[b]	40.12 ± 17.90 *n* = 53	55.57 ± 19.58 *n* = 21	0.002[b]
EQ-VAS scores baseline	67.91 ± 12.70	69.18 ± 16.64	0.662[b]	68.52 ± 14.67	76.62 ± 14.81	0.002[b]

[a]Unless stated otherwise
[b]Student's *t*-test
[c]Chi-Square test

3.2. Internal consistency

The MSISQ-15 showed a good internal consistency with Cronbach's alpha's of >0.8 for test and retest in MS patients, SCI patients, and total patient group (Table 2). The internal consistencies for the domains were adequate with Cronbach's alpha's of >0.7 in the total patient group and MS patients. In the SCI patients, the primary domain showed a moderate internal consistency with a Cronbach's alpha of 0.53 (test) and 0.55 (retest). The internal consistency for the secondary and tertiary domains was good.

TABLE 2. Cronbach's alpha reflects the internal consistency for the MSISQ-15 total and subscale scores.

	MS ***n*** **= 53**		**SCI** ***n*** **= 49**		**Total patient group** ***n*** **= 102**	
	Test	**Re-test**	**Test**	**Re-test**	**Test**	**Re-test**
MSISQ-15 total score	0.90	0.91	0.82	0.84	0.87	0.88
MSISQ-15 domains						
Primary	0.79	0.78	0.53	0.55	0.70	0.69
Secondary	0.76	0.82	0.79	0.80	0.77	0.81
Tertiary	0.89	0.93	0.89	0.93	0.89	0.93

3.3. Reproducibility

The average test-retest period was 20.3 ± 13.8 days, 30.2 ± 25.7 days, 25.1 ± 20.9 days for MS patients, SCI patients, and total patient group, respectively. The ICCs for agreement for the total MSISQ-15 and the three domains in MS patients, SCI patients, and total patient group were all higher than 0.7, indicating an adequate reliability (Table 3). Table 3 lists the LOA ranges of the total MSISQ-15 and the domains.

3.4. Criterion validity

A significant relationship was found between the total score of MSISQ-15 and the total score of PISQ-12 in females of the patient group (test: r=-0.682; retest: r=-0.649, Table 4). In the male study population, the patient group showed a significant relationship between the total score of MSISQ-15 and the total score of IIEF-15 (test: r=-0.446; retest: r=-0.405, Table 4).

TABLE 3. The reproducibility is presented in terms of intraclass correlation coefficient (ICC) and limits of agreement (LOA).

	MS, *n* = 53			SCI, *n* = 49			Total patient group, *n* =102		
	Change (mean ± SD)	ICC (95 % CI)	LOA[a]	Change (mean± SD)	ICC (95 % CI)	LOA[a]	Change (mean ± SD)	ICC (95 % CI)	LOA[a]
MSISQ-15 total score	0.11 ± 6.26	0.88 (0.79-0.93)	-12.16 to 12.38	0.53 ± 5.18	0.88 (0.79-0.93)	-9.62 to 10.68	0.31 ± 5.74	0.88 (0.82-0.92)	-10.94 to 11.57
MSISQ-15 domains									
Primary	0.13 ± 2.06	0.90 (0.84-0.94)	-3.90 to 4.16	0.37 ± 1.89	0.88 (0.79-0.93)	-3.34 to 4.07	0.25 ± 1.97	0.90 (0.86-0.93)	-3.62 to 4.11
Secondary	0.23 ± 3.30	0.75 (0.60-0.85)	-6.24 to 6.69	0.18 ± 2.79	0.83 (0.71-0.90)	-5.28 to 5.65	0.21 ± 3.05	0.79 (0.70-0.85)	-5.77 to 6.18
Tertiary	-0.25 ± 2.83	0.86 (0.77-0.92)	-5.80 to 5.31	-0.02 ± 3.10	0.83 (0.72-0.90)	-6.09 to 6.05	-0.14 ± 2 .95	0.85 (0.78-0.90)	-5.92 to 5.65

[a]Calculated as: y=mean(change) ± 1.96 x standard deviation (change)

TABLE 4. Criterion validity of the MSISQ-15 with the PISQ-12 (in females), IIEF-15 (in males), and EQ-VAS.

	Patients (test)			Patients (retest)		
	rho[a]	*P*-value	Number	rho[a]	*P*-value	Number
MSISQ-15 vs. PISQ-12	-.682	<0.001	49	-.649	<0.001	49
MSISQ-15 vs. IIEF-15	-.446	0.001	53	-.405	0.003	53
MSISQ-15 vs. EQ-VAS	-.513	<0.001	102	-.428	<0.001	102

[a] Pearson's correlation coefficient

3.5. Construct validity

All predefined hypotheses were confirmed:

1. The reference group did indeed have lower MSISQ-15 scores than the patient group (Table 1).

2. and 3. Female patients with lower PISQ-12 scores and male patients with lower IIEF-15 indeed had higher MSISQ-15 scores (criterion validity).

4. In the patient group a significant correlation was found between the MSISQ-15 score and the EQ-VAS (Table 4). This confirmed the hypothesis: "patients who score higher on the EQ-VAS will have lower MSISQ-15 scores".

3.6. Floor and ceiling effects

In the patient group, no floor effects were seen for the total score, primary domain, and secondary domain (Table 5). Floor effects were seen in the tertiary domain (19% of the patients). Ceiling effects were absent in the patient group.

In the reference group, floor effects were found in all the domains (24-46%). Six (12%) reference persons had the lowest possible total score. No ceiling effects were found in the reference group.

TABLE 5. Floor and ceiling effects at baseline for the patient and reference groups

	Patients *n* = 102		**References *n* = 50**	
	Floor	**Ceiling**	**Floor**	**Ceiling**
MSISQ-15 total score	1 (1%)	0 (0%)	6 (12%)	0 (0%)
MSISQ-15 domains				
Primary	3 (3%)	0 (0%)	12 (24%)	0 (0%)
Secondary	10 (10%)	0 (0%)	23 (46%)	0 (0%)
Tertiary	19 (19%)	3 (3%)	21 (42%)	0 (0%)

4. DISCUSSION

After linguistic validation of the original English MSISQ-15 into the Dutch language, we validated its use for patients with MS and spinal cord disorders such as SCI and

cauda equina syndrome. The measurement properties showed this Dutch version of the MSISQ-15 to be valid, reliable, and consistent. This enables physicians to assess the influence of symptoms of neurological disease on sexual activity and satisfaction in patients in clinical practice and in research settings.

The quality of PRO measures for sexual function in neurological patients was assessed in a recently published systematic review.[3] Strong evidence was found only for the MSISQ-15/-19 for patients with MS. PRO measures for patients with SCI showed mostly poor to fair quality and re-evaluation of all measurement properties was advised.[3] In view of this we chose to validate the Dutch MSISQ-15 not only in patients with MS, but also in patients with SCI and cauda equina syndrome. In all these three conditions, interruption of the spinal cord or the pelvic autonomic nerves interferes with genital engorgement, erections, ejaculation, and climax.[1,16] Besides the similarity between the influence of symptoms on sexual function, the similarity in treatment suggests that the instrument might work well in those populations.

The good internal consistency of the Dutch MSISQ-15 with Cronbach's alpha's ranging from 0.82 to 0.91 for (re)test and patient (sub)groups (Table 2) is comparable with that of the original MSISQ-15 (total Cronbach's $\alpha = 0.92$, primary domain $\alpha = 0.87$, secondary domain $\alpha = 0.82$, tertiary domain $\alpha = 0.91$).[5] The Cronbach's alpha's of all subdomains were adequate, except for the primary domain in the spinal cord disorder group (0.53-0.55). The original design of the primary domain focuses on "MS-related-neurologic changes" that may directly affect sexual feeling or response. In the spinal cord disorder group a moderate correlation of the items in the primary domain was found. This could have been caused by the specific well-known problems in SCI patients such as dissociation between desire, erection, ejaculation, and orgasm.[16] Another explanation for the moderate correlation could be the more severe disease-related disability in patients with a spinal cord disorder. However, during the face-to-face interviews (linguistic validation process) the SCI patients did not mention any irrelevant or missing items. Overall, the internal consistency of the total MSISQ-15 score remains good.

The reproducibility for the Dutch MSISQ-15 in terms of test-retest scores was excellent. The mean change between test-retest was ± 0.31 points, demonstrating adequate agreement. We found an ICC for agreement of 0.88 for the 15 items of the Dutch translation of the MSISQ-15, indicating good reliability. Comparison with other studies was not possible, a test-retest was neither performed in the original MSISQ-15 study[5] nor in the MSISQ-19 study[4].

Patients and references were good distinguishable as shown by the confirmation of predefined hypotheses, confirming discriminative ability and therewith good criterion validity. Furthermore, confirming its use to specifically deal with sexual problems faced by patients with neurological disease.

No ceiling effects were found in patients or references. As expected, floor effects were present in all domains in the reference group (24-42%). Still, only 6 (12%) references had the lowest possible MSISQ-15 total score. Remarkable is the floor effect of the tertiary domain in the patient group (19%). The tertiary domain items measure the psychological aspects of SD. Possible explanations for a lowest score are the duration or acceptance of living with a neurological disease and having a stable relationship. This could lead to a reduced reliability and could have effects on the responsiveness.[12] Still the reliability was found to be good (ICC tertiary domain 0.85, Table 3).

Analyzing the responsiveness and interpretability of the MSISQ-15 was not possible because of the short follow-up. Another limitation of our study was the lack of a golden standard. In the absence of a validated Dutch measure of sexual function in neuro-urological patients, we used the PISQ-12 in women and the IIEF-15 in men. Additionally, the IIEF-15 assesses erectile dysfunction over the last month in contrast to the last six months of the MSISQ-15. Lastly, treating physicians were asked to recruit all consecutive patients meeting the inclusion criteria, but we do not know what proportion actually participated and what were the reasons for non-participation.

One of the strengths of our study was the use of standardized measurement properties to evaluate the reliability and validity of the MSISQ-15, proposed by Terwee et al.[12] Furthermore, our study design also allowed testing the MSISQ-15 in patients with spinal cord disorders. The results support the usability of the measure in this population, except when using the primary domain as subscale on itself. In general, MSISQ-15 outcomes may support the patient and physician to discuss SD. We recommend the Dutch physicians to use this measure in both research and clinical practice to evaluate SD in patients with MS and spinal cord disorders. Providing that the result of the primary domain in patients with spinal cord disorders should be cautiously handled because of the moderate internal consistency. To assess the urogenital function in neuro-urological patients we advise to use the MSISQ-15 combined with the SF-Qualiveen. The SF-Qualiveen is a questionnaire validated in Dutch to evaluate the urinary-specific quality of life in MS or SCI patients.[17,18]

5. CONCLUSIONS

In conclusion, this Dutch version of MSISQ-15 was tested following well-established guidelines on measurement properties and showed good validity and reliability. The MSISQ-15 allows us to evaluate SD in patients with MS and spinal cord disorders in both research and clinical practice.

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SUPPLEMENTARY MATERIAL: The Dutch version of the MSISQ-15

MSISQ-15: vragenlijst over intimiteit en seksualiteit bij multiple sclerose (MS) of een dwarslaesie

INSTRUCTIES: Deze vragenlijst wordt gebruikt om de impact van multiple sclerosis (MS) of een dwarslaesie op intimiteit en seksualiteit beter te kunnen begrijpen. U wordt gevraagd aan te geven hoe verschillende klachten van MS of een dwarslaesie invloed hebben op uw intimiteit en seksualiteit de afgelopen 6 maanden.
De vragen kunt u beantwoorden door één vakje achter de vraag aan te kruisen of aan te vinken. Er zijn geen goede of foute antwoorden. Als u twijfelt over uw antwoord, kiest u dan het voor u best passende antwoord.

DE AFGELOPEN ZES MAANDEN VORMDEN DE VOLGENDE KLACHTEN EEN BELEMMERING VOOR MIJN SEKSUELE ACTIVITEIT OF TEVREDENHEID:

(Kruis één vakje per regel aan)	nooit	bijna nooit	soms	bijna altijd	altijd
1. spierstijfheid of krampen in mijn armen, benen of lichaam	☐	☐	☐	☐	☐
2. blaas- of plasklachten	☐	☐	☐	☐	☐
3. darmklachten	☐	☐	☐	☐	☐
4. trillen of schudden van mijn handen of lichaam	☐	☐	☐	☐	☐
5. pijn, branderig of ongemakkelijk gevoel in mijn lichaam	☐	☐	☐	☐	☐
6. het gevoel dat mijn lichaam minder aantrekkelijk is	☐	☐	☐	☐	☐
7. het gevoel minder mannelijk of vrouwelijk te zijn vanwege MS/dwarslaesie	☐	☐	☐	☐	☐
8. minder gevoel of gevoelloosheid in mijn geslachtsdelen	☐	☐	☐	☐	☐
9. angst om seksueel afgewezen te worden vanwege MS/dwarslaesie	☐	☐	☐	☐	☐
10. bezorgdheid of ik mijn partner seksueel kan bevredigen	☐	☐	☐	☐	☐
11. minder vertrouwen in mijn seksualiteit vanwege MS/dwarslaesie	☐	☐	☐	☐	☐
12. gebrek aan seksuele interesse of seksueel verlangen	☐	☐	☐	☐	☐
13. minder intense of plezierige orgasmen of hoogtepunten	☐	☐	☐	☐	☐
14. het duurt te lang om een orgasme of hoogtepunt te krijgen	☐	☐	☐	☐	☐
15. - vagina niet nat of vochtig genoeg (vrouwen)/ - problemen om een goede erectie te krijgen of te houden (mannen)	☐	☐	☐	☐	☐

CHAPTER 7

Urotherapy in children with dysfunctional voiding and the responsiveness of two condition-specific questionnaires

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ABSTRACT

Aims: We sought to establish the responsiveness of the Dutch Vancouver Symptom Score for Dysfunctional Elimination Syndrome (VSSDES) and Pediatric urinary incontinence Quality of life (PinQ) questionnaires. Secondary, we evaluated the outcome of urotherapy extended for children with dysfunctional voiding (DV).

Methods: This cross-sectional multicenter study was done in one tertiary and two community hospitals. Children with DV were included, also when refractory to previous urotherapeutic treatment. The questionnaires were completed before and after urotherapy. The primary outcome measure was the responsiveness of the Dutch VSDESS and PinQ. Secondary outcome was the initial success (defined by the International Children's Continence Society) of extended urotherapy.

Results: Between June 2014 and May 2016, 64 children (median age 7 years, IQR 6-10) received urotherapy (median 18 weeks, IQR 11-28). In contrast to the VSSDES, the PinQ showed good responsiveness. For children and parents, respectively, the area under the ROC-curve was 0.79 ($P = 0.01$) and 0.72 ($P = 0.03$) for the PinQ and 0.50 ($P = 0.98$) and 0.55 ($P = 0.62$) for the VSSDES. Fifty children received extended urotherapy, 27 had complete, and 14 had partial response. Sixteen children had been refractory to previous treatment; four showed complete and six showed partial response.

Conclusion: The PinQ is able to detect clinically important changes in continence-specific quality of life after treatment. We support the use of the VSSDES questionnaire in addition to the current diagnostics for the diagnosis of DV. Extended urotherapy showed to be a successful treatment for children with DV, also for those who had received previous unsuccessful treatment.

1. INTRODUCTION

Lower urinary tract symptoms (LUTS) are a common reason for children to visit the pediatrician or pediatric urologist.[1-3] Symptoms related to the voiding and storage phase of bladder can contribute to numerous functional elimination disorders.[3,4] Dysfunctional voiding (DV) is a common cause of LUTS in neurologically intact children.[4] Voiding symptoms such as straining, hesitancy, dysuria, and storage symptoms such as frequency, urgency, or incontinence are suggestive for DV.[3-5] Furthermore, DV is often associated with recurrent urinary infections, and bowel dysfunction such as constipation or fecal incontinence.[5,6] The symptoms of DV can have a negative impact on a child's quality of life and self-esteem.[1,2,6] The International Children's Continence Society (ICCS) has defined DV as habitual contractions of the urethral sphincter or pelvic floor during voiding. The uroflowmetry curve demonstrates a staccato pattern with or without an interrupted flow concomitant with activity on EMG.[4,5] The exact epidemiology of DV is unknown.[5] The prevalence of DV in the general population has a wide range: 4.2% - 46.4%.[5,6]

Urotherapy and pelvic muscle floor retraining can be a successful treatment in the majority of these children.[3,6] Urotherapy is a non-standardized conservative based treatment option for children with voiding dysfunctions.[4,5] According to the ICCS, urotherapy includes education about lower urinary tract anatomy and function, as well as life-style advices (balanced fluid intake, diet, proper voiding posture without holding maneuvers, regular bladder and bowel emptying patterns).[4,5] During follow up the child will be encouraged to comply with therapy and the LUTS will be monitored by bladder, bowel and intake diary.[4,5] Urotherapy can be extended with visual biofeedback by two approaches: feedback of the uroflow curve and teaching perineal muscle identification by EMG electrodes.[1,3,5,6] The physical therapist can extend the urotherapy with pelvic floor muscle retraining, which implies learning how to relax the pelvic floor during voiding.[1,3-6]

Administering a condition-specific questionnaire can be useful to evaluate LUTS and effect of the treatment. Subjective complaints can be translated objectively into a total score.[4] Two English-language questionnaires were translated into Dutch and proved to have good validity and reliability. One is the Pediatric urinary incontinence Quality of life score (PinQ), which measures the continence-specific quality of life in children with bladder dysfunction.[7,8] The other is the Vancouver Symptom Score for Dysfunctional Elimination Syndrome (VSSDES), which evaluates the symptoms of patients with DV.[9]

In the study presented here we followed children with DV during their treatment. Our primary aim of this study was to evaluate the responsiveness of the Dutch-language versions of the VSSDES and PinQ. Secondary, we evaluated the results of extended urotherapy.

2. MATERIALS AND METHODS

2.1 Study design and population

The local ethics committee approved this multicenter prospective cross-sectional study (MEC-2014-290). Children with the age between 4 and 17 years presenting with DV at the pediatric, pediatric urology, or pelvic floor physical therapy outpatient clinics at two community hospitals and one tertiary hospital in the Netherlands between June 2014 and May 2016 were eligible for inclusion in the study. Children who had a previous unsuccessful treatment in a different setting were included as well. Patients with a neurogenic disease, anatomic abnormalities of the urinary tract, and previous urological surgery were excluded. The diagnosis DV was based on clinical symptoms, and a staccato and/or intermittent uroflowmetry with increased activity on pelvic floor EMG. After signing informed consent, patients, and parents were asked to fill out the questionnaires twice: after inclusion and after finishing urotherapy.

2.2 Questionnaires

Prior to urotherapy, patients and parents filled out the VSSDES and the PinQ.

The VSSDES is a 14-item condition-specific measure to evaluate the symptoms of bladder and bowel dysfunction. The last question addresses the ease with which the questionnaire can be completed, and the response to this question is excluded from the total score. Responses are given on a 5-point Likert scale, ranging from zero (no complaints) to four (severe symptoms) except for question 3 about voiding frequency (5-6 times: score of 0; 3-4 times or 7-8 times: score of 2; 1-2 times or >8: score of 4). All items are weighted equally. A total score is obtained by summating the item scores; the higher the total score the more severe the symptoms.[10] A cutoff score of 11 is established for the Dutch version.[9]

The PinQ is a 20-item questionnaire to evaluate the quality of life of children with urinary incontinence. All items are scored on a 5-point Likert scale. A higher total score corresponds with a lower quality of life.[8] Incompletely filled out questionnaires were accepted if no more than two answers were missing. Then the total score is calculated by multiplying the number of items in the questionnaire by the mean value of responses

to the answered questions. No cutoff score is published for the PinQ. Thibodeau et al[2] made an assumption to grade the severity of impact on quality of life: mild <20, moderate 21-50, and severe >51.

After urotherapy had finished, patients, and parents again filled out the VSSDES and the PinQ and answered an additional question derived from the RAND-36-Item Health Survey (RAND 36-HTI): "How is your voiding problem compared to one year ago?" (response categories: much better, somewhat better, about the same, somewhat worse, much worse).[11]

2.3 Outcome measure questionnaires

The primary outcome measure of this study was the responsiveness of the two questionnaire's. A questionnaire's responsiveness is its ability to detect clinically important changes over time in patients when treatment is given. A measure of the responsiveness is the area under the receiver operating characteristic (ROC) curve (AUC), according to an external criterion. The answer to the question derived from the RAND 36-HTI and the initial outcome served as external criteria. The AUC shows the ability of a questionnaire to discriminate between improvement and no improvement. An AUC of at least 0.7 was considered to reflect adequate responsiveness.[12]

2.4 Urotherapy

Our secondary objective was to evaluate the outcome of "extended" urotherapy. All included children received "standard" urotherapy consisting of initial evaluation, education, and management as described by the ICCS.[4] Standard urotherapy with visual biofeedback by uroflowmetry and EMG electrodes and/or retraining of the pelvic floor was defined as "extended" urotherapy.

In one of the community hospitals only standard urotherapy was given. Children visited the pediatrician combined with a trained nurse once or twice. When standard urotherapy failed children returned to the outpatient clinic of the pediatrician for additional treatment with medication or were referred to a physical therapist.

Children included in the tertiary hospital and in the other community hospital received extended urotherapy given by a trained nurse or physical therapist. Those children had approximately 5-7 sessions in 4 months. During this period the children were discussed 2-3 times with the pediatrician or pediatric urologist. When additional treatment with anticholinergics was needed because of persistent urgency with acceptable post void residual urine, the pediatrician or pediatric urologist started tolterodine (slow release) 2 mg 1 daily, or solifenacine 5 mg 1 daily, or oxybutynine 0.4 mg/kg 3 daily for 4-12

weeks. The use of anticholinergics was re-evaluated with the pediatrician or pediatric urologist during urotherapy. After approximately four months urotherapy was finished. When extended urotherapy failed an invasive treatment as botulinum toxin A injections into the bladder wall or into the urethral sphincter could be considered. Injections in the urethral sphincter were given when an increased activity of pelvic floor muscles or external urethral sphincter was seen during voiding on urodynamic study. A total of 100 IU of botulinum toxin A was injected in equal dose into the external sphincter at the 3, 9 and 12 o'clock positions under general anesthesia and antibiotic prophylaxis. For boys a cystoscope was used. The transurethral approach to the sphincter is more difficult for girls, therefore injections were placed paraurethral.[13] In cases of persisted symptoms of an overactive bladder without post void residual urine botulinum toxin A injections (total dose of 70 UI) into the bladder wall were given under general anesthesia and antibiotic prophylaxis by cystoscopy.

2.5 Outcome measures extended urotherapy

The outcome of extended urotherapy was defined by the definition of initial success proposed by the ICCS: no response (<50% reduction of LUTS), partial response (50 to 99% reduction of LUTS), and complete response (100% reduction of LUTS).[4] The children who received only standard urotherapy were excluded in this evaluation. The initial success and symptoms were evaluated after the last visit of urotherapy. The initial success and effect on symptoms of an invasive treatment (botulinum toxin A injections) were not evaluated. Data such as symptoms, post void residual, urinary frequency, maximum voided volume, and fluid intake before urotherapy and at the last visit of urotherapy were retrospectively collected. The maximum voided volume was retrieved from the voiding chart and refers to the largest volume voided, excluding the first morning void. The maximum voided volume was considered small or large if <65% or >150% of expected bladder capacity (EBC), respectively.[4] The EBC was defined by the formula (30 x [age in years + 1]mL).[4] The maximum level was 390 mL at 12 years.[4]

2.6 Statistical analysis

Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY). A two-sided *P*-value <0.05 was considered significant. Descriptive statistics were calculated and are presented as median (interquartile range [IQR]), frequency and percentiles. To evaluate differences in symptoms and results of the two questionnaires between before and after treatment, the paired-samples *t*-test and the McNemar test were used for continuous and categorical variables, respectively. One-way analysis of variance (ANOVA) was used for the evaluation of more than two independent groups. The answer on the RAND 36-HTI question was dichotomized to "not improved"

(including "about the same", "somewhat worse" and "much worse") and "improved" (including "much better" and "somewhat better"). The AUC was calculated to determine the responsiveness.[12]

3. RESULTS

The study population consisted of 64 children with dysfunctional voiding and their parents. Fifty children received extended urotherapy with or without pelvic floor retraining. The fourteen children who received standard urotherapy where only included to evaluate the responsiveness of the questionnaires. Patient characteristics are displayed in Table 1.

TABLE 1. Patient characteristics of the study population presented as number (%) or median (interquartile range)

Study population *n* = 64	
Age, median (IQR)	7 (6-10)
Number of girls, *n* (%)	35 (55)
Duration of the treatment in weeks, median (IQR)	18 (11-28)
Type of urotherapy, *n* (%)	
Standard urotherapy	14 (22)
Extended urotherapy	50 (78)
Extended urotherapy *n* = 50	
Age, median (IQR)	8 (7-10)
Number of girls, *n* (%)	28 (56)
Duration of the treatment in weeks, median (IQR)	18 (11-25)
Anticholinergics during urotherapy, *n* (%)	14 (28)

3.1 Questionnaires

The VSSDES questionnaire was completed before and after urotherapy by 50 (78%) children and 49 (77%) parents; the PinQ by 45 (70%) children, and 48 (75%) parents. Table 2 presents the mean difference scores (SD).

TABLE 2. Total mean score (SD) of the VSSDES or PinQ questionnaire before and after urotherapy and the difference between.

Total score of the questionnaire	Before urotherapy	After urotherapy	Difference	*P*-value
VSSDES[b]				
Child *n = 50*	17.9 ± 6.9	11.6 ± 5.9	-6.3 ± 6.7	<0.001[a]
Parent *n = 49*	17.9 ± 6.5	11.5 ± 6.2	-6.4 ± 6.6	<0.001[a]
PinQ[c]				
Child *n = 45*	23.7 ± 14.8	17.0 ± 15.0	-6.7 ± 10.9	<0.001[a]
Parent *n = 48*	21.5 ± 11.2	17.1 ± 12.9	-4.4 ± 12.0	0.015[a]

[a] Paired t-test
[b] A higher total score indicates more severe symptoms.
[c] A higher total score indicates a lower quality-of-life.

The responsiveness of the VSSEDS was measured by the AUC calculated with the RAND-36-HTI as an external criterion; the AUC was 0.50 ($P = 0.98$) for children and 0.55 ($P = 0.62$) for parents. The AUC for the PinQ was 0.79 ($P = 0.01$) for the children and 0.72 ($P = 0.03$) for the parents (Table 3).

3.2 Outcome of extended urotherapy

Fifty children received extended urotherapy with or without pelvic floor retraining (Table 1). Sixteen children were refractory to previous urotherapeutic treatment and received urotherapeutic treatment in a different setting for the second time. Fourteen of them had received previous urotherapeutic treatment in combination with pelvic floor physical therapy and two had received group urotherapy. The median duration of urotherapy was 18 weeks (IQR 11-25 weeks).

After extended urotherapy symptoms such as daytime and nighttime incontinence, urge, dysuria, and abdominal pain all had improved significantly (Table 4). During urotherapy anticholinergics were prescribed to fourteen children. After urotherapy, 64% of the children had stopped the anticholinergics. Before treatment three girls experienced urinary tract infections (UTIs) with fever (≥2 in 6 months) and nine girls and one boy had UTIs without fever (frequency: 1-3 UTIs in 12 months, five girls unknown). During therapy, none of the children experienced UTIs. The mean fluid intake increased from 985 mL to 1547 mL ($P < 0.001$, $n = 43$). A voiding chart was completed at the last visit of urotherapy in 34 children. Nineteen out of 34 children had a maximum voided volume <65% or >150% of the EBC before therapy, fourteen children showed improvement after treatment. At the last visit of urotherapy 37 children had undergone an uroflowmetry, which in 12 (32.4%) of them showed a persistent staccato and/or

intermittent flow pattern. In 7 of those 12 children also with increased activity on pelvic floor EMG. The mean post void residual of these 37 children decreased from 28.1 mL to 12.8 mL ($P = 0.025$).

TABLE 3. The VSSDES and PinQ scores (SD) and their corresponding RAND-36-HTI response reflect the responsiveness. The RAND-36-HTI functions as an external criterion.

VSSDES	Number (%)	mean ± SD[a]
RAND-36-HTI *n = 50*		
Much better/ a little better	41 (82.0)	-6.3 ± 7.0
Same	7 (14.0)	-6.5 ± 5.9
Much worse/a little worse	2 (4.0)	-5.5 ± 2.1
Area under the ROC curve		0.50
***P*-value**		0.98
Parent RAND-36-HTI *n = 49*		
Much better/ a little better	38 (77.5)	-6.8 ± 6.3
Same	9 (18.4)	-6.8 ± 8.0
Much worse/a little worse	2 (4.1)	2.0 ± 1.4
Area under the ROC curve		0.55
***P*-value**		0.62
PinQ	**Number (%)**	**mean ± SD[b]**
RAND-36-HTI *n = 45*		
Much better/ a little better	37 (82.2)	-8.3 ± 11.2
Same	6 (13.3)	-0.9 ± 4.3
Much worse/a little worse	2 (4.5)	5.5 ± 7.8
Area under the ROC curve		0.79
***P*-value**		0.01
Parent RAND-36-HTI *n = 48*		
Much better/ a little better	37 (77.1)	-6.7 ± 11.0
Same	9 (18.8)	1.1 ± 12.4
Much worse/a little worse	2 (4.1)	14.5 ± 5.0
Area under the ROC curve		0.72
***P*-value**		0.03

[a] A higher total score indicates more severe symptoms.
[b] A higher total score indicates a lower quality-of-life.

Based on the definition initial success by the ICCS, the treatment outcome of extended urotherapy could be classified as complete response in 27 (54%), partial response in 14 (28%), and no response in 9 (18%) children (Table 5). There was a significance difference in urotherapy outcome between the children refractory to previous urotherapeutic treatment and those who received urotherapeutic treatment for the first time, in disadvantage of the children refractory to previous urotherapeutic treatment ($P = 0.014$). Overall, nine out of 50 children had no response to extended urotherapy. Three children

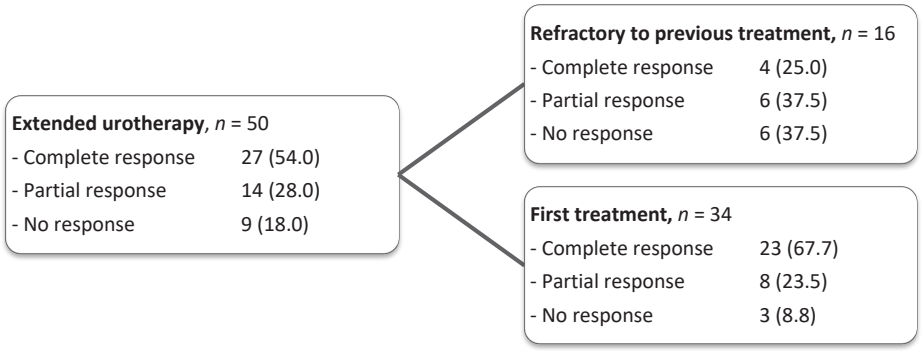
and their parents decided to accept the situation. Six children received botulinum toxin A injections in the urethral sphincter (n = 4), or in the bladder wall (n = 1), or in the urethral sphincter and bladder wall (n = 1).

TABLE 4. Symptoms before and after urotherapy presented as number (%)

Symptoms n = 50[a]	Before urotherapy n (%)	After urotherapy n (%)	P-value
Daytime incontinence	42 (84.0)	23 (46.0)	<0.001[b]
- Partial success (50-99%)		12 (24.0)	
- No success (< 50%)		11 (22.0)	
Dry	8 (16.0)	27 (54.0)	
Nighttime incontinence	30 (60.0)	16 (32.0)	<0.001[b]
- Partial success (50-99%)		3 (6.0)	
- No success (< 50%)		13 (26.0)	
Dry	20 (40.0)	34 (68)	
Urge (n = 43)	21 (48.8)	6 (14.0)	<0.001[b]
Dysuria	3 (6.0)	0	
Abdominal pain	10 (20.0)	2 (4.0)	0.008[b]

[a] Unless stated otherwise.
[b] McNemar test.

TABLE 5. Initial success following the three ICCS basics principles of treatment outcomes presented as number (%).



4. DISCUSSION

The evaluation of the responsiveness of the VSSDES and PinQ, and of patient outcomes suggest that the PinQ questionnaire can detect clinically important changes over time (Table 3) and that symptoms had improved after extended urotherapy (Table 4).

The reliability and validity of the original and Dutch versions of both questionnaires were found to be good in earlier studies.[7-10] Completing the questionnaires makes the symptoms and feelings transparent and negotiable with the health professional and family-members. This could lead to increased empathy, support, and treatment compliance. Both, Afshar et al and Bower et al, suggest to measure the responsiveness of the questionnaires.[7,10] As far as we know, this is the first study that reports on the responsiveness of the questionnaires. We hypothesized that lower post-treatment scores on the PinQ and the VSSDES compared to the baseline scores would reflect improvements on quality of life and symptoms. According to the external criterion, the RAND-36-HTI question: "How is your voiding problem compared to one year ago?", the AUC was measured. The responsiveness of both the child and parent versions of the PinQ proved to be more than adequate, the AUC was both above >0.7. This was not the case for the VSSDES. Perhaps the RAND-36-HTI question solely addresses the aspect of the voiding dysfunction and does not fully encompass the symptoms. Besides, only two parents and children found the voiding dysfunction to be worse now. We noted that completing the post-treatment questionnaires was not a priority for the parents and children. Resulting in a median interval of 14 weeks (IQR 0-48) between ending urotherapy and completing the last questionnaires.

In this study, the Dutch VSSDES showed to be not useful to detect clinical important changes over time in symptoms after therapy. Still, the questionnaire is a reliable and valid tool to more objectively and systematically evaluate symptoms of patients with DV.[9] Our hypothesis for the PinQ could be confirmed. The children and parents who answered the RAND-36-HTI question with "much" or "somewhat better" had mean lower scores on the PinQ after treatment.

The children in our study showed a good initial success rate after extended urotherapy with visual biofeedback by uroflowmetry and EMG electrodes and/or pelvic floor retraining. Judged from three ICCS basic principles of treatment outcomes, extended urotherapy was successful for 82% (complete response 54%) of the children overall. The success of treatment in children who were refractory to previous urotherapy was 63% (complete response 25%). Children who did not respond to previous urotherapy may be more motivated in new and different setting. It is also possible that the moment

and the intensity of attention by the healthcare professional or parent is relevant to success. Previous studies have reported success rates of 90-100% of urotherapy with the possibility to extend with biofeedback or pelvic floor retraining or medication (commonly an antimuscarinic) in children with DV.[5,14] Tugtepe et al[15] reported on 28 children with DV refractory to three months of standard urotherapy. All children received additional extended urotherapy resulting in 50-100% decrease of LUTS. The outcome of the present study is comparable or slightly less favorable than that of these previous studies, to which the multicenter design and the inclusion of 16 children refractory to a previous treatment may have contributed. Note, however, outcomes of urotherapy are hard to compare between studies with different study populations, treatment approaches, and definitions of success of DV. In our study, the children have received standard urotherapy as defined by the ICCS extended with visual biofeedback by uroflowmetry and EMG electrodes and/or retraining of the pelvic floor. If needed an additional treatment with anticholinergics was started to treat urge-related symptoms. The content of extended urotherapy was similar, despite every child need his or her own stepwise approach. The role of pharmacological therapy can be considered as ancillary in the management of DV.[3,5] A standard protocol for urotherapy following a stepwise approach and uniform reporting of outcomes would be helpful in current clinical practice and facilitate comparison between studies.

One of the strengths of this study is the prospective inclusion of all eligible children and the use of a standard measure to evaluate the responsiveness.[12] Children were recruited in different hospital settings and received different types of urotherapy, which makes the results of this study more generalizable for current clinical practice. However, the different approaches of urotherapy could possibly give some bias on the outcome. Limitations include the absence of a control group, the retrospective collection of LUTS data and the long interval between finishing urotherapy and completing the last questionnaires, which may have confounded the results.

5. CONCLUSION

In contrast to the VSDESS, the PinQ is a responsiveness questionnaire. The PinQ is able to detect clinically important changes over time when treatment is given and can be used initially, during follow up and after treatment to evaluate the continence-specific quality of life in children with DV. We support the use of the VSSDES questionnaire in addition to the current diagnostics (voiding diary and uroflowmetry with pelvic floor

EMG) for the diagnosis of DV. Urotherapy with visual biofeedback by uroflowmetry and EMG electrodes and/or retraining of the pelvic floor showed to be a successful treatment for children with DV, also for those who had received previous unsuccessful treatment.

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PART IV

General discussion and summary

CHAPTER 8

General discussion

In this general discussion, the main findings of this thesis are presented and placed in perspective with the current literature. Furthermore, the future perspectives for clinical practice and research are given.

MAIN FINDINGS

Evidence based outcome of surgical treatments of anatomic bladder outlet obstruction in the neurogenic population

The systematic review of **chapter 2** an overview of the current literature on the outcome of different surgical therapies for the treatment of anatomic bladder outlet obstruction in males with neurogenic bladder dysfunction. The types of anatomic bladder outlet obstruction discussed are benign prostate obstruction, urethral stricture, and bladder neck sclerosis. The most important recommendation for clinical practice is that a urodynamic study to determine the exact type of lower urinary tract (LUT) dysfunction should not lack in the work-up of bladder outlet obstruction in neuro-urological (NU) patients. Identifying the optimal practice was impossible due to limited availability of high-quality studies.

Outcome of bladder outlet procedures in children with neurogenic urinary incontinence

In **chapter 3** the long-term outcome on continence of bladder outlet procedures, such as bladder neck reconstruction and bladder neck sling, in 60 children with mainly myelomeningocele as etiology of neurogenic urinary incontinence are discussed. After a median follow-up of 10.4 years, continence rate was modest to good (77%, without urinary leakage for minimum of 4 hours), although re-intervention was required in 42% to achieve this result. The re-interventions consisted of redo of the bladder outlet procedure, other type of outlet procedure, bulking agents, bladder augmentation and bladder neck closure. The definition of urinary continence used in the literature varies and makes comparison of outcome with other studies difficult. In view of the young age of the patient population, awareness of the outcome on the long term is valuable for patient counseling and to create awareness in patients and parents about what to expect.

Outcome of adjustable continence balloons in men with stress urinary incontinence

The outcome of adjustable continence balloons (ProACT) in the treatment of stress urinary incontinence after radical prostatectomy and transurethral resection of the

prostate (TURP), respectively in **chapter 4** and **chapter 5,** are evaluated. We evaluated results in terms of achieving continence, changes in pads use, complications, re-interventions and patient-reported estimates of improvement assessed with the Patient Global Impression of Improvement (PGI-I) scale. The PGI-I scale is an index that provides an overall response to an intervention.[1] All procedures, 143 patients post radical prostatectomy with a median follow up of 46 (IQR 21-76) months, were performed by the same surgeon in Rotterdam in the study of **chapter 4**. After implantation, daily pad usage had decreased significantly from a median of 3.5 (IQR 2.0-5.0) pads per day preoperatively to a median of 1.0 (IQR 0.0-2.0) pads per day at 6 months and 0.0 (IQR 0.0-2.0) pads per day at 1 year. At the end of follow up 30% needed a re-intervention. The results of 29 post-TURP patients with a follow-up of 21 (IQR 11-43) months are presented in **chapter 5**. Adjustable continence balloons were implanted by two surgeons, in 24 patients in Rotterdam and in 5 patients in Rome. The daily pad usage decreased significantly from a median of 3.5 (IQR 2.3-5.3), pads per day preoperatively to a median of 1.0 (IQR 1.0-1.9) pads per day at 6 months and 1.0 (IQR 0.0-2.5) pads per day at 1 year. Twenty-four percent had a re-intervention at the end of follow-up.

Both studies showed a clear beneficial continence outcome in patients with adjustable continence balloons in the treatment of stress urinary incontinence post radical prostatectomy and post-TURP. On the long term, the majority of the patients reported improvement on the PGI-I scale and perceived improvement ≥50% on daily pad use on the long term.

Validity of the Dutch version of a patient reported outcome measure for sexual function in neuro-urological patients

In **chapter 6** the translation and validation process of the Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-15) for the use in Dutch patients with multiple sclerosis (MS) and spinal cord injury (SCI) is described. This self-report measure consists of 15 questions evaluating the influence of MS symptoms on sexual activity and satisfaction over the preceding 6 months.[2] Standardized guidelines were used to translate the questionnaire from English to Dutch.[3] Subsequently, a standardized assessment of the measurements properties was performed.[4] The internal consistency, i.e. the correlations between the items in the questionnaire, was adequate for total score and domains. The reproducibility was good, as shown from a comparison of the total MSISQ-15 scores at baseline and 1-2 weeks later. Patients' MSISQ-15 scores were correlated with severity of symptoms of sexual dysfunction measured with reference standards (PISQ-12[5] in women and IIEF-15[6] in men) and confirmed positive rating for criterion validity. MSISQ-15 scores in patients were higher than in references indicating good construct

validity. This study confirms that the Dutch version of the MSISQ-15 is a reliable and valid measure to evaluate symptoms of sexual dysfunction in patients with MS or with SCI.

Responsiveness of two patient reported outcome measures and outcome of urotherapy in children with dysfunctional voiding

The Dutch version of the Vancouver Symptom Score for Dysfunctional Elimination Syndrome (VSSDES) questionnaire can be used to evaluate symptoms of bladder and bowel dysfunction.[7] The Dutch version of the Pediatric urinary incontinence Quality of life (PinQ) questionnaire evaluates the quality of life of children with urinary incontinence.[8] In **chapter 7** the responsiveness, its ability to detect clinically important changes over time, of the VSSDES and PinQ questionnaires is tested in 64 children with dysfunctional voiding. The responsiveness of the PinQ proved to be good, in contrast to the VSSDES. However, the VSSDES questionnaire is still a reliable and valid tool to more objectively and systematically evaluate symptoms of patients with dysfunctional voiding and therefor a useful tool in addition the current diagnosis (voiding diary and uroflowmetry with pelvic floor EMG) for the diagnosis of dysfunctional voiding. The PinQ questionnaire can be used at baseline, during follow up and after treatment to evaluate the continence-specific quality of life in children with dysfunctional voiding. Besides the responsiveness, **chapter 7** describes the outcome on LUT symptoms of extended urotherapy in 64 children with dysfunctional voiding. Urotherapy is a non-standardized conservative treatment for children with voiding dysfunctions, consisting of initial evaluation, education, and management. When urotherapy is combined with visual biofeedback by uroflowmetry and EMG electrodes and/or retraining of the pelvic floor it is defined as extended urotherapy. The majority of children had 50-100% response on LUT symptoms after extended urotherapy, also for those who had received previous unsuccessful treatment.

THERAPY OUTCOMES WITHIN FUNCTIONAL UROLOGY

Three aspects from clinical practice: patient, physician and evidence

In general, the first step in healthcare is to clarify the patient's demand of medical assistance. Why does a patient approach a physician? What issue is the most bothersome? Good patient-physician communication is key to identifying a patient's needs, perceptions and expectations. Besides, communication helps to create an interpersonal relationship, and facilitates exchange of medical information and involving the patient in making decisions.[9] In short, communication is essential to create a bridge between patient and physician.

Patients with LUT and/or pelvic floor dysfunction may experience symptoms in one or more than one of the following domains: urinary, anorectal, sexual dysfunction and pelvic organ prolapse. The aim of a treatment is commonly to reduce relevant symptoms and improve quality of life. To achieve this, the most optimal practice should be identified per individual, preferably in agreement with the patient's preferences. Treatment outcomes studies, systematic reviews and guidelines (often based on systematic reviews), are helpful to identify best practice.

In 'evidence based medicine', individual clinical expertise is integrated with the best available external clinical evidence to enable decision-making about the care of individual patients.[10,11] Evidence based medicine focuses on educating physicians in understanding and critical appraisal of published literature to optimize clinical care, including the science of systematic reviews and the development of clinical practice guidelines.[10,11] By clinical experience, physicians may obtain the capability to effectively harmonize patients' need and preferences in treatment.[10] The best external clinical evidence refers to clinically appropriate studies aimed to answer a clinical question. Thus, apart from randomized trials and meta-analyses, the answer may come from basic science research and also from clinical studies.[10] A quality appraisal of the found evidence, including the risk of various biases, determines the level of evidence and affects the strength of recommendation.[11]

Through time, evidence alone has been recognized to have some limitations; it needs to be combined with patient values, preferences, and circumstances to provide shared decision-making.[11] In the process of shared decision-making, the physician shares information and supports patients to deliberate and express their preferences.[12] This may lead to a well-considered decision and tests why a patient would prefer this decision above other treatment options. With this intent, conversations between patient and physician are an important environment to explore evidence, clinical experience and preferences.

Evidence of effective treatment within function urology

Systematic reviews on treatment efficacy, such as the one described in **chapter 2**, aim to build evidence by combining outcomes of different studies. Valid comparison of outcomes of different studies is often hampered by limitations, like a weak study design and different terminologies and parameters of outcome used. A uniform parameter is essential to perform meaningful meta-analyses and consistently compare outcome of different studies and treatments. Organizations such as the International Consultation on Incontinence (ICI) and International Continence Society (ICS) recommend the use of subjective and objective measurements in outcome studies involving patients with

LUT dysfunction.[13,14] Examples of subjective measures are patient reported outcome measures (PROMs) obtained by means of questionnaires. Objective measures are, for example, voiding diaries, pad test, and urodynamics. Nevertheless, the most appropriate outcome parameter is not provided. Two recent reviews presented an overview of different outcome measures of cure used in the evaluation of surgical treatments of stress urinary incontinence in NU patients[15] and non-neurogenic patients[16]. Both reviews found a heterogeneity in subjective (patient reported) and objective (traditional) outcome parameters defining cure and were not able to obtain consensus.[15,16]

Appropriate outcome measures to define treatment efficacy

As mentioned above, an important focus of treatment in functional urology is reducing symptoms and improving quality of life.[17,18] Reaching consensus about the most appropriate outcome measures might be complicated by differences in perception between physician and patient, and between patients. In other healthcare domains, the treatment outcome is more obvious. For example, the outcome in treatment of cardiovascular diseases or cancer is often survival. When it comes to urinary incontinence, a patient's perception of successful treatment outcome may range from being completely dry to reducing a half of daily pad use. Also, the impact of a certain degree of urinary incontinence on quality of life might be different between patients, not to mention the physicians' perceptions of treatment outcome. This supports and encourages to collect PROMs, besides traditional outcomes.

Furthermore, in the field of functional urology it is important to distinguish NU patients from non-NU patients and to distinguish adults from children. Although reducing LUT symptoms and improving quality of life is commonly the focus of treatment in these populations, factors such as an underlying diseases or patient age may interfere with the management and the most suitable outcome measures. To illustrate this, outcome measures in children should be adapted to age and understanding capacity. In the evaluation of NU patients, extra attention must be paid to preserve upper urinary tract and possible effects of the neurological condition on bladder function.

In the cohort studies on efficacy of adjustable continence balloons (**chapters 4 & 5**), we used the PGI-I as a subjective measure to evaluate patients' overall response to the intervention, besides objective measures such as pad use, re-interventions and complications. Urotherapy was evaluated by two PROMs, VSDESS and PinQ, and by data on symptoms gathered at outpatient visits, including voiding diary, uroflowmetry and post void residual (**chapter 7**). Bladder outlet procedures in children with neurogenic incontinence were retrospectively reviewed based on objective measures retrieved from medical files (**chapter 3**). No PROMs were used in this retrospective study. Overall,

these studies on treatment efficacy contribute to building evidence. Important to note, in all these studies comparison with the literature was challenging due to inconsistent use of outcomes. Thus, to improve comparison of treatments within functional urology, consensus should be reached how to define the outcome, assuming that heterogeneity of the population is taken into account when comparing outcomes. There seems to be a role for both a traditional outcome measure (objective) and a PROM (subjective). However, until consensus is reached, a clear definition of outcome should be given in the study methods.

PATIENT REPORTED OUTCOME MEASUREMENTS WITHIN FUNCTIONAL UROLOGY

Added value and possible implications of patient reported outcome measures

PROMs have been developed to quantify patients' perspective of their health condition, including the functional status and the impact on symptoms and quality of life. These measurable subjective perspectives can be a valuable tool at different points during patient care. First, PROMs can be used as diagnostic instrument or as baseline measurement to assess a patient's perception and impact of symptoms on one's daily activities. Second, the disease progression can be monitored with PROMs as standardized measures. Lastly, PROMs can be used as an outcome measure in the evaluation of a certain treatment - both in clinical practice and in research setting.

Shared decision-making is a result of patient-centered communication and evidence based medicine.[19] In evidence based medicine the use of PROMs is well established, for example as treatment outcome measure. PROMs may facilitate physician-patient communication and promotes shared decision-making.[20] When completing PROMs, the patient is encouraged to reflect on his or her health condition. This process gives the patient the opportunity to gain a deeper understanding on the condition, enabling to discuss relevant issues to discuss with the physician.[21] Completion could lead to clarification of a patient's own perception and informs the physician about the patient's perspective, which may give insights on the presence and intensity of prominently symptoms. Clarification of the most bothersome symptoms experienced by an individual patient helps the physician to adequate manage expectations about treatment effectiveness. The patient should be able to make an informed decision with an assessment of risk and benefit of all treatment options in light of own circumstances. This might impact a patient's treatment choice and improve treatment compliance and satisfaction with health care. Beside improving clinical management of individual

patients as motive for routine use in clinical practice, comparison of outcomes and comparing the provider performances have been driven motives.[22] The possible added value of PROMs has not gone unnoticed in functional urology. Several international and national guidelines have recognized the importance of PROMs and recommend their use besides traditional outcome measures.[23-26]

Requirements of patient reported outcome measures before implementation

A PROM should not be implemented before its measurement properties have been evaluated by a standardized validation process.[4] When a PROM is used in a specific population it must be confirmed that it has an adequate validity and measures the underlying construct in that population. In the Netherlands, several valid PROMs are available to assess non-neurogenic patients' perceptions of the domains of LUT and pelvic floor disorders.[5,27-30] The use of condition-specific questionnaires is recommended in the assessment of NU patients, although these are not yet available in Dutch for each domain. The urinary-specific quality of life in NU patients can be measured with the Dutch SF-Qualiveen.[31,32] Until recently, a Dutch validated PROM to evaluate symptoms of sexual dysfunction in NU patients was not available. The Dutch version of the MSISQ-15 was found reliable and valid to evaluate symptoms of sexual dysfunction in patients with MS or with SCI (**chapter 6**). When using a PROM in the evaluation of treatment effectiveness, the PROM must be sensitive to clinical change. This property can be established by testing its responsiveness (**chapter 7**).

The implementation of valid and reliable PROMs in routine clinical practice faces several challenges. Time-consuming collection of information should be minimized by providing short and easy to understand PROMs. To achieve high rates of patient participation, audience-specific PROMs and innovative approaches are required, particularly regarding children, elderly, and sicker patients. Digitally provided PROMs have the potential to improve the routine use of PROMs. An additional benefit of digital PROMs is the possibility of accurate transfer of data into a patient's electronic medical chart. With regard to the health professionals, defining cut-off scores and minimally important change of PROMs helps to increase the ease of interpretation and adapt management if necessary. The minimally important change represents the smallest change in score that is noticeable to the patient and perceived as important to the patient.[33] For example, the International Prostate Symptom Score (IPSS), a symptom assessment questionnaire in the management of benign prostatic obstruction, categorizes scores as mild, moderate, and severe symptoms.[34,35] Barry et al[36] succeeded to determine the minimally important change of the IPSS. Namely, a three-point improvement on the IPSS was the minimum change corresponding with slight improvement on symptoms noticed by a patient.[36]

The same study showed correlations between five points improvement on IPSS and moderate improvement on symptoms, and between eight points improvement on IPSS and marked improvement on symptoms.[36]

OPTIMIZATION OF PATIENT CARE IN FUNCTIONAL UROLOGY

Patient care in functional urology might be optimized by building bridges between patients, physicians, and researchers. This is seen in the interdependence of evidence based medicine and shared decision-making.[19] Added value is given to evidence based medicine by comparing treatment effectiveness, analyzing treatment efficacy reflected by traditional outcome measures and PROMs, and validating PROMs. In view of this thesis, Figure 1 presents our contributions to optimize patient care. Figure 1 is based on and adapted to a figure of Hoffman et al[19], which presents the intersection of evidence based medicine and patient-centered communication.

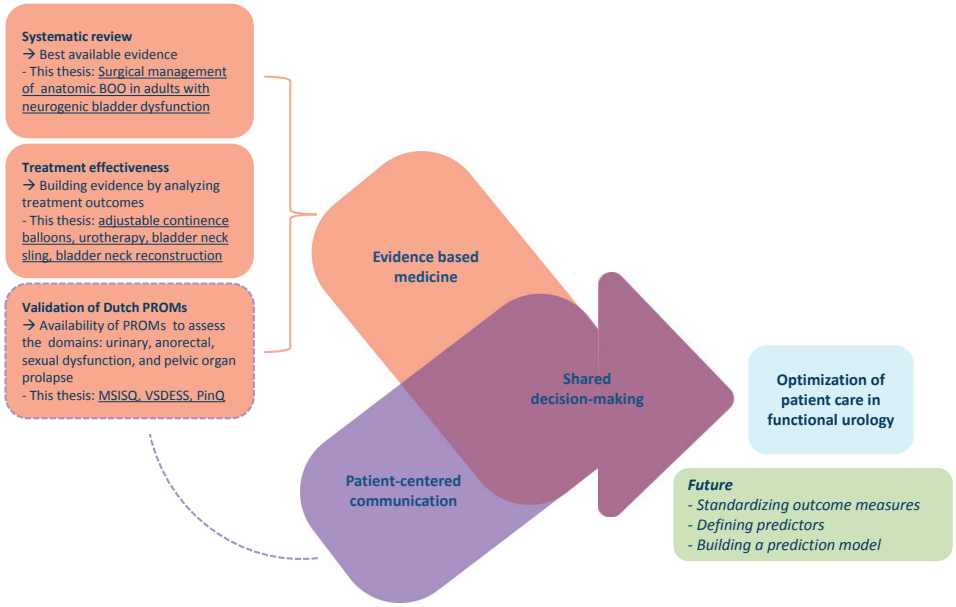

FIGURE 1. Our contributions to optimize care.

Outcome predictors in treatments of functional urology

The possibility to identify the best treatment in an individual in advance would be valuable and improve personal-based trade off prior to treatment. Identification of variables that predict outcome of an intervention gives insight if a patient will or will not respond to a specific treatment and might initiate a different treatment choice in this patient. Different predictors should be combined in a multivariate model to accurately predict the outcome of treatment. Building a prediction model for functional urology, similar to the prostate cancer risk calculator[37], is still in its early stages. Outcomes of different treatments in functional urology need to be available and outcome measures should be standardized. Future research in the field of functional urology should focus on identifying these predictors and treatment outcome measures, PROMs might play a key role as outcome parameter or as predictor in a model.

FUTURE PERSPECTIVES

PROMs may identify the domain (urinary, anorectal, sexual dysfunction, and pelvic organ prolapse) with the most impact on patient wellbeing and function (diagnostic) and may play an important role in informing treatment decisions and as outcome measure. Our research group has succeeded in making available validated Dutch PROMs to assess the domains of LUT and pelvic floor disorders in non-neurogenic patients. Regarding Dutch neurogenic patients, urinary-specific quality of life can be evaluated with the SF-Qualiveen and sexual function and satisfaction with the MSISQ-15. A PROM about anorectal symptoms is still lacking. Our next step will be the translation and validation of the neurogenic bowel dysfunction (NBD) score to measure bowel complaints and fecal incontinence in neurogenic patients.[38] Furthermore, the ease of use, as well as the ease of interpretation and implementation of PROMs in clinical practice can be further improved. Additionally, PROMs may give the opportunity to further develop value based care i.e., health care driven by health outcomes per euro spent.[39]

Adequately informing the patient about the expected treatment outcomes is one of the essentials in shared decision-making. Besides treatment outcomes in terms of cure, possible adverse events or complications or re-interventions should be discussed. Future studies with treatment outcomes aim to build evidence within functional urology. Intervention studies with long-term follow-up in large cohorts are preferred. Until consensus is reached on the most adequate outcome parameter or outcome parameter set, we advise the combined use of PROMs and traditional outcome measures.

In the treatment of male stress urinary incontinence different devices (e.g. artificial urinary sphincter, male sling, adjustable continence balloons) are available. High quality studies evaluating efficacy are lacking. These studies have a wide variation in study design, follow-up, patient population, and biases. Therefore defining the best treatment option and drawing meaningful conclusions is difficult.[40] A future prospective comparative study evaluating the efficacy of artificial urinary sphincter, male sling, and adjustable continence balloons in this population would be helpful. PROMs as study endpoint could have an additional value, besides others, like pad count, one hour pad test, and complication rates. Suggested validated PROMs assessing the impact of urinary incontinence on quality of life pre- and post-operative settings are UDI-6 and IIQ-7. Additionally, an overall response of treatment can be provided with the PGI-I. The outcomes of these PROMs can be compared between the groups, assuming that groups are homogenous and results are stratified based on predictive factors (such as neurological diseases and radiation therapy). A study design like this shows the combined use of PROMs and traditional outcome measures to evaluate the efficacy of an intervention. The next step could be to define preoperative cut-off scores of the UDI-6 and the IIQ-7, and other predictors, such as patient characteristics or pre-operative pad count, to develop a prediction model in order to predict the most effective treatment outcome per individual.

Identifying the optimum treatment in an individual has the potential to improve shared decision-making. Future research is needed to establish standardized outcome of different treatments and identification of variables that predict outcome in functional urology. Perhaps PROMs might play a key role as outcome parameter or as predictor in a model, as described in the example above. The possibility of optimizing patient care in functional urology could be a prediction model. Currently, our research group is developing a multivariate model that aimed to predict treatment outcome of female urge urinary incontinence based on patient history, patient characteristics and investigations.[41]

EPILOGUE

In view of improving shared decision-making in functional urology, this thesis aimed at adding value to evidence based medicine by comparing treatment effectiveness, analyzing treatment efficacy reflected by traditional outcome measures and by PROMs, and validating PROMs. PROMs have the potential, in addition to traditional outcome measures, to quantify a patient's perspective of the LUT and/or pelvic floor dysfunction. Before implementation of Dutch PROMs in clinical practice, the adequacy

of its psychometric measurement properties should have been established. Combining evidence based medicine with shared decision-making by building bridges between patients, physician, and researcher contributes to optimization of clinical practice.

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CHAPTER 9

Summary & Samenvatting

SUMMARY

Functional disorders of the lower urinary tract (LUT), which consists of the urinary bladder and its sphincters, and the pelvic floor, are characterized by symptoms in one or more than one of the following domains: urinary, anorectal, sexual dysfunction, and pelvic organ prolapse. Symptoms of LUT and pelvic floor disorders can have a negative impact on the quality of life. **Chapter 1**, the general introduction of this thesis, describes the background and assessment of symptoms of LUT and pelvic floor disorders, and outcome measures used in the evaluation of treatment efficacy. Nowadays, various patient reported outcome measures (PROMs) are available to capture patients' perspectives of health, disease, and effect of intervention. The aim of this thesis is to evaluate effectiveness of conservative and surgical treatment in functional urology, reflected by traditional and patient reported outcome measures.

In the first part of this thesis, **chapter 2**, different surgical therapies for the treatment of anatomic bladder outlet obstruction in males with neurogenic bladder dysfunction were evaluated in order to identify an effective treatment. This systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions. In general, it appears that surgical management of anatomic bladder outlet obstruction may result in urinary incontinence. The types of anatomic bladder outlet obstruction discussed are benign prostate obstruction, urethral stricture, and bladder neck sclerosis. Identified surgical therapies are transurethral resection of the prostate (TURP) in patients with Parkinson disease or spinal cord injury (SCI) or cerebrovascular accident, endoscopic treatment of urethral stricture by laser ablation or urethrotomy in mainly SCI patients, and bladder neck resection in SCI patients. The outcome of TURP may be highly variable, from persistent or de novo urinary incontinence, regained normal micturition control, to urinary continence. In studies on bladder neck resection and endoscopic urethrotomy good results were seen. Laser ablation and cold knife urethrotomy resulted in restarting intermittent catheterization or adequate voiding. Due to the limited availability of high-quality studies it was impossible to identify the optimal practice. Nonetheless, the most important recommendation for clinical practice is that a urodynamic study to determine the exact type of LUT dysfunction should not lack in the work-up of bladder outlet obstruction in neuro-urological (NU) patients.

In the second part of this thesis the outcome of different surgical therapies to achieve urinary incontinence are described.

Achieving continence in children with urinary incontinence is a challenge, especially incontinence secondary to neurogenic sphincteric deficiency. When non-surgical

therapy such as anticholinergic medications and intermittent catheterization fails, a surgical therapy could be considered. In **chapter 3**, the long-term outcome on continence of bladder outlet procedures, such as bladder neck reconstruction and bladder neck sling, in children with neurogenic urinary incontinence are discussed. The patient's needs, gender, and bladder function and the surgeon's preference has influence on the choice of a bladder outlet procedure with or without concomitant surgery such as bladder augmentation and continent catheterizable urinary channel. A bladder neck reconstruction increases bladder outlet resistance by lengthening and narrowing the urethra with tubularization of the trigone. The bladder neck sling procedure was based on coaptation, elevation, and narrowing of the urethra by suspension of the bladder neck by placing an autologous rectus fascial strip around the bladder neck and fixing the ends to the pubic symphysis. In view of the young age of the patient population, awareness of the outcome on the long term is important, but scientific reports are sparse. In this study, 60 children with mainly myelomeningocele as etiology of neurogenic urinary incontinence, underwent a bladder outlet procedure. After a median follow-up of 10.4 years, continence rate was modest to good (77%, without urinary leakage for minimum of 4 hours), although re-intervention was required in 42% to achieve this result. The re-interventions consisted of redo of the bladder outlet procedure, other type of outlet procedure, bulking agents, bladder augmentation and bladder neck closure. Comparison with other studies in the literature is difficult because of the different modifications of surgery techniques used, alternated concomitant surgery, small number of patients analyzed, varying time of follow-up (the majority short term), and different definitions of urinary continence. Those long-term results are valuable for patient counseling and to create awareness in patients and parents about what to expect.

In men with non-neurogenic stress urinary incontinence, it is mostly associated with prostatectomy, such as incontinence post radical prostatectomy (RP) or incontinence post-TURP. The next step after failure of conservative therapy or drug treatment is a surgical intervention. Besides male sling and artificial urinary sphincter, a minimally invasive option may be chosen, in particular, the adjustable continence balloons (ProACT™). The outcome of adjustable continence balloons in the treatment of stress urinary incontinence after RP and TURP, respectively in **chapter 4** and **chapter 5,** are evaluated in terms of achieving continence, changes in pads use, complications, re-interventions and patient-reported estimates of improvement assessed with the Patient Global Impression of Improvement (PGI-I) scale. The PGI-I scale is an index that provides an overall response to an intervention.

In **chapter 4** the outcome of 143 patients post-RP with a median follow up of 46 (IQR 21-76) months are described. Patients with an artificial urinary sphincter or male sling in situ and those with a history of adjuvant radiotherapy after RP were excluded. All procedures were performed by the same surgeon in Rotterdam. After implantation, daily pad usage had decreased significantly from a median of 3.5 (IQR 2.0-5.0) pads per day preoperatively to a median of 1.0 (IQR 0.0-2.0) pads per day at 6 months and 0.0 (IQR 0.0-2.0) pads per day at 1 year. At the end of follow up 30% needed a re-intervention. After a median follow up of 56 (IQR 28-79) months, 112 patients had the adjustable continence balloons in situ and answered the questionnaire with their daily pad use and PGI-I scale. A ≥50% reduction in daily pad use was seen in 64%, the dry rate was 45%, and 87% perceived improvement on the PGI-I scale.

In **chapter 5** the results of 29 post-TURP patients with a follow-up of 21 (IQR 11-43) months are presented. To our knowledge, this is the first study reporting results of post-TURP patients separately. The adjustable continence balloons were implanted by two surgeons, in 24 patients in Rotterdam and in 5 patients in Rome. The daily pad usage decreased significantly from a median of 3.5 (IQR 2.3-5.3), pads per day preoperatively to a median of 1.0 (IQR 1.0-1.9) pads per day at 6 months and 1.0 (IQR 0.0-2.5) pads per day at 1 year. Twenty-four percent had a re-intervention at the end of follow-up. Twenty-three patients completed the questionnaire with their daily pad use and PGI-I scale after a median follow-up of 28 (IQR 13-63) months. Outcome on continence had improved in 65%, with a ≥50% reduction in daily pad use, including 26% dry rate. Improvement on the PGI-I scale was reported by 96%.

To summarize both studies, adjustable continence balloons showed a clear beneficial continence outcome in patients with stress urinary incontinence. The majority of the patients were satisfied and perceived improvement ≥50% on daily pad use on the long term.

In the third part of this thesis the translation and validation of a PROM for sexual function in NU patients is described (**chapter 6**) and the responsiveness of two PROMs to assess LUT function in children is studied (**chapter 7**).

In the Netherlands, several PROMs to assess patients' perception of the domains of LUT and pelvic floor disorders in non-neurogenic patients are widely available. In the assessment of NU patients, the use of condition-specific questionnaires is recommended, although these are not yet available in Dutch for each domain. The urinary-specific quality of life in NU patients can be measured with the Dutch SF-Qualiveen. A Dutch PROM to measure bowel complaints and fecal incontinence in neurogenic patients, such

as the neurogenic bowel dysfunction score, is missing. Until recently, a Dutch validated PROM to evaluate symptoms of sexual dysfunction in NU patients was not available. The Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-15) demonstrated the most adequate measurements properties compared to other PROMS evaluating sexual function in neurologic patients. This self-report measure consists of 15 questions evaluating the influence of multiple sclerosis (MS) symptoms on sexual activity and satisfaction over the preceding 6 months. Although the MSISQ-15 was originally developed for MS patients, the similarity between the sexual dysfunction symptoms of patients with MS and those with SCI, as well as the similarity in treatment, suggests that the instrument might work well in both populations. The objective of our study was to provide and validate a Dutch version of the MSISQ-15 for the use in MS and SCI patients (**chapter 6**). The MSISQ-15 was translated from English into Dutch according to standardized guidelines. Sexual active patients with MS or SCI were asked to complete the MSISQ-15 and PISQ-12 (women) or IIEF-15 (men) at baseline and 1-2 weeks later. A reference group without a neurological condition recruited at a general medical practice completed the questionnaires once. Afterwards, standardized assessment of the measurements properties was performed. The correlations between the items in the questionnaire was adequate for total score and domains (internal consistency). The reproducibility was good, as shown from a comparison of the total MSISQ-15 scores at baseline and 1-2 weeks later. Patients' MSISQ-15 scores were correlated with severity of symptoms of sexual dysfunction measured with reference standards (PISQ-12 in women and IIEF-15 in men) and confirmed positive rating for criterion validity. MSISQ-15 scores in patients were higher than in references indicating good construct validity. This study confirms that the Dutch version of the MSISQ-15 is a reliable and valid measure to evaluate symptoms of sexual dysfunction in patients with MS or with SCI.

The responsiveness of a questionnaire is its ability to detect clinically important changes over time. So, does the questionnaire measure changes if they have really occurred. In the assessment of the LUT function in children two Dutch PROMs are available: the Vancouver Symptom Score for Dysfunctional Elimination Syndrome (VSSDES) questionnaire and Pediatric urinary incontinence Quality of life (PinQ) questionnaire. The VSSDES can be used to evaluate symptoms of bladder and bowel dysfunction. The PinQ evaluates the quality of life of children with urinary incontinence. Those two Dutch questionnaires showed to be reliable and valid, but the responsiveness was, until recently, unknown. The responsiveness of the PinQ proved to be good in children with dysfunctional voiding, in contrast to the VSSDES (**chapter 7**). This confirms the PinQ can be used at baseline, during follow up and after treatment to evaluate the continence-specific quality of life in children with dysfunctional voiding. The VSSDES is still a reliable and valid questionnaire to more objectively and systematically evaluate symptoms of

patients with dysfunctional voiding and therefor a useful tool in addition the current diagnostics (voiding diary and uroflowmetry with pelvic floor EMG) for the diagnosis of DV. Besides the responsiveness, **chapter 7** describes the outcome on LUT symptoms of extended urotherapy in children with dysfunctional voiding. Urotherapy is a non-standardized conservative treatment for children with voiding dysfunctions, consisting of initial evaluation, education, and management. When urotherapy is combined with visual biofeedback by uroflowmetry and EMG electrodes and/or retraining of the pelvic floor it is defined as extended urotherapy. The majority of children had 50-100% response on LUT symptoms after extended urotherapy, also for those who had received previous unsuccessful treatment.

In the general discussion, **chapter 8**, the added value to evidence based medicine by comparing treatment effectiveness, analyzing treatment efficacy reflected by traditional outcome measures and by PROMs, and validating PROMs is discussed. All chapters of this thesis contribute to evidence based medicine. The combination of evidence based medicine with shared decision-making contributes to optimization of clinical practice. In order to improve comparison of treatments within functional urology, consensus should be reached how to define the outcome. A role for both a traditional outcome measure (objective) and a PROM (subjective) are suggested. Finally, the future perspectives of standardization of outcomes and the possibility of a prediction model in functional urology are discussed.

SAMENVATTING

De functionele urologie is het gedeelte van de urologie welke zich richt op functiestoornissen van de lage urinewegen en de bekkenbodem. Deze functiestoornissen kunnen zich presenteren met klachten uit één of meer van de volgende domeinen: plasklachten, anorectale klachten, seksuele dysfunctie en prolaps. Deze symptomen kunnen een negatieve invloed hebben op de kwaliteit van leven. In **hoofdstuk 1**, de introductie van dit proefschrift, wordt de achtergrond van deze domeinen beschreven. Daarnaast worden verschillende uitkomstmaten om het effect van een behandeling binnen de functionele urologie te evalueren toegelicht. Het doel van dit proefschrift is het evalueren van de effectiviteit van conservatieve en chirurgische behandelingen binnen de functionele urologie. De effectiviteit wordt gereflecteerd door traditionele uitkomstmaten en patiënt gerapporteerde uitkomstmaten (PROMs).

Het geslacht, de leeftijd, en de aanwezigheid van een neurologische aandoening kan van invloed zijn op de mate van ernst en hinder van symptomen en op de behandeling van een dysfunctie aan de lage urinewegen en/of bekkenbodem. In het eerste gedeelte van dit proefschrift, **hoofdstuk 2**, wordt in een systematische review de effectiviteit van verschillende chirurgische behandelingen van een anatomische blaasuitgangsobstructie vergeleken in mannen met een neurogene blaas. De chirurgische behandeling van een anatomische blaasuitgangsobstructie kan mogelijk leiden tot urine-incontinentie, wat een vervelende complicatie is. De anatomische blaasuitgangsobstructies die worden besproken zijn: een goedaardige prostaat obstructie, een urethrastrictuur en sclerose van de blaashals. De chirurgische behandelingen die werden geïdentificeerd zijn een transurethrale resectie van de prostaat (TURP), een blaashalsresectie en een endoscopische behandeling van een urethrastrictuur door middel van laser ablatie of een urethrotomie. De uitkomsten van een TURP bij mannen met de ziekte van Parkinson, een dwarslaesie of een cardiovasculaire aandoening varieerden van persisterende of de novo urine-incontinentie tot urine continentie. Goede resultaten werden gezien in de studies die de uitkomsten na blaashalsresectie en urethrotomie evalueerden. In deze studies werden de resultaten van voornamelijk mannen met een dwarslaesie getoond. Zowel laser ablatie als een cold knife urethrotomie resulteerde in adequate mictie of de mogelijkheid tot het hervatten van zelfkatheterisatie. Door de gelimiteerde beschikbaarheid van goede kwaliteitsstudies was het niet mogelijk de meest optimale behandeling te identificeren. Er wordt geadviseerd bij een neuro-urologische patiënt een urodynamisch onderzoek te verrichten om de exacte blaasfunctiestoornis te identificeren alvorens een blaasuitgangsobstructie te behandelen. Deze systematische review geeft een overzicht van de huidige literatuur en benadrukt de noodzaak tot verder wetenschappelijk onderzoek binnen deze neurogene patiëntenpopulatie.

In deel II van dit proefschrift worden de uitkomsten van verschillende chirurgische behandelingen van urine-incontinentie beschreven.

Het is een uitdaging om bij kinderen met urine-incontinentie continentie te bereiken. In het bijzonder wanneer dit secundair is aan neurogene sfincterdeficiëntie. Een chirurgische behandeling kan worden overwogen wanneer een niet-chirurgische behandeling als anticholinergica of intermitterende katheterisatie faalt. In **hoofdstuk 3** worden de langetermijnresultaten van blaashalschirurgie, zoals blaashalsplastiek en fascieslingprocedure, op continentie bij kinderen met neurogene urine-incontinentie beschreven. Het doel van blaashalschirurgie is de uitgangsweerstand van de blaas te verhogen. Bij een blaashalsplastiek wordt door middel van tubularisatie van een strook blaaswand de urethra vernauwd en verlengd. De fascieslingprocedure is gebaseerd op elevatie, coaptatie en vernauwing van de urethra door een strook rectusfascie rond de blaashals te positioneren. Blaashalschirurgie kan worden gecombineerd met een blaasaugmentatie en het aanleggen van een continent katheteriseerbaar stoma. Gezien de jonge leeftijd van deze patiëntenpopulatie zijn lange termijn uitkomsten belangrijk. In deze studie worden de uitkomsten van blaashalschirurgie bij zestig kinderen met voornamelijk myelomenigocele als etiologie van neurogene urine-incontinentie geëvalueerd. Een periode van minimaal vier uur zonder urine lekkage werd gedefinieerd als continentie. Na een follow-up van mediaan 10.4 jaar, was 77% van de kinderen droog. Een re-interventie was nodig in 42% van de kinderen. Re-interventies die zich voordeden waren het opnieuw uitvoeren van de blaashalschirurgie, een andere blaashalsprocedure, bulking agents, blaasaugmentatie en het sluiten van de blaashals. Het vergelijken van deze resultaten met de resultaten van andere studies is moeilijk vanwege verschillende gebruikte chirurgische technieken, variërende follow-up en verschillende definities van continentie. De gepubliceerde langetermijnresultaten zijn waardevol bij de bespreking van de verschillende behandelopties met patiënt(e) en zijn/haar ouders en geven inzicht in de mogelijke verwachtingen van blaashalschirurgie.

Niet-neurogene urine-incontinentie bij mannen is meestal geassocieerd met een ingreep aan de prostaat, bijvoorbeeld urine-incontinentie na een radicale prostatectomie of een TURP. Indien een conservatieve en/of medicamenteuze behandeling in deze patiëntenpopulatie faalt is de volgende stap een chirurgische interventie. Aanpasbare continentietherapie middels ProACT™-ballonnen is een minimaal invasieve behandeloptie naast de male sling en de artificiële urinaire sfincterprothese. De aanpasbare continentieballonnen worden percutaan geïmplanteerd, zodat zich aan de rechter- en linkerzijde van de urethra één ballon bevindt. Twee titanium ventielen, aan elke kant van het scrotum één, staan in verbinding met de periurethrale ballon aan de desbetreffende zijde. Na de implantatie kan het volume van de ballonnen poliklinisch

worden aangepast om een zo optimaal mogelijk evenwicht tussen continentie en de mogelijkheid tot mictie te bereiken. De subcutane ventielen kunnen met een naald via het scrotum worden aangeprikt. De uitkomsten van aanpasbare continentieballonnen in de behandeling van stress urine-incontinentie na een radicale prostatectomie of een TURP worden, respectievelijk, in **hoofdstuk 4** en in **hoofdstuk 5**, geëvalueerd. Er wordt gekeken naar de resultaten op gebied van succes, gebruik van incontinentie-inleggers, complicaties, re-interventies en patiënt gerapporteerde subjectieve verbetering verkregen middels de Patient Global Impresson of Improvement score (PGI-I). De PGI-I score is een PROM die inzicht geeft in de mate waarin de behandeling verbetering heeft gebracht van de klachten. De patiënt geeft dit aan op een zevenpuntsschaal ('heel veel slechter' tot en met 'heel veel beter').

De uitkomsten van de aanpasbare continentie ballonnen bij 143 mannen met urine-incontinentie na een radicale prostatectomie worden in **hoofdstuk 4** beschreven. De mediane follow-up was 46 (interkwartielafstand (IQR) 21-76) maanden. Mannen met in de voorgeschiedenis adjuvante radiotherapie en mannen met een male sling of een artificiële urinaire sfincterprothese in situ werden geëxcludeerd. Alle ballon-implantaties werden verricht in Rotterdam door één operateur. Het incontinentie-inlegger gebruik daalde significant van mediaan 3.5 (IQR 2.0-5.0) inleggers/dag peroperatief naar mediaan 1.0 (IQR 0.0-2.0) inleggers/dag zes maanden postoperatief en vervolgens naar mediaan 0.0 (IQR 0.0-2.0) inleggers/dag één jaar postoperatief. Aan het einde van de follow-up had 30% een re-interventie nodig. Een vragenlijst naar het inlegger gebruik en de PGI-I score werd na een mediane follow-up van 56 (IQR 28-79) maanden door 112 patiënten met de aanpasbare incontinentieballonnen in situ ingevuld. Bij 64% van de patiënten werd een halvering of meer op het dagelijks inlegger gebruik gezien, bij 45% werd continentie bereikt en 87% gaf verbetering op de PGI-I score aan.

In **hoofdstuk 5** worden de resultaten van aanpasbare continentieballonnen bij 29 patiënten post-TURP gepresenteerd. De follow-up bedroeg 21 (IQR 11-43) maanden. Voor zover bekend, is dit de eerste studie die resultaten van post-TURP-patiënten apart evalueert. De aanpasbare continentieballonnen werden door twee verschillende operateurs verricht, de implantatie vond bij 24 patiënten in Rotterdam plaats en bij 5 patiënten in Rome. Het dagelijks gebruik van incontinentie-inleggers daalde significant van 3.5 (IQR 2.3-5.3) inleggers/dag preoperatief, naar 1.0 (IQR 1.0-1.9) inleggers/dag zes maanden postoperatief en vervolgens naar 1.0 (IQR 0.0-2.5) inleggers/dag één jaar postoperatief. Gedurende de follow-up was een re-interventie bij 24% van de patiënten nodig. Drieëntwintig patiënten hebben de vragenlijst ingevuld na een mediane follow-

up van 28 (IQR 13-63) maanden. Verbetering van ≥50% op het dagelijks inlegger gebruikt werd gezien bij 65% van de patiënten, inclusief 26% continente patiënten. Verbetering op de PGI-I score werd door 96% van de patiënten gerapporteerd.

Samenvattend, beide studies laten zien dat aanpasbare continentieballonnen een positief effect hebben op de continentie bij patiënten met stress urine-incontinentie. Op de lange termijn is de meerderheid van de patiënten tevreden en ervaart een verbetering van ≥50% op het dagelijks inlegger gebruik.

Deel III van dit proefschrift gaat over patiënt gerapporteerde uitkomstmaten, oftewel PROMs. Het vertaalproces en de validatie van een PROM wordt beschreven voor gebruik in Nederland (**hoofdstuk 6**). Daarnaast wordt de responsiviteit getoetst van twee PROMs (**hoofdstuk 7**).

Om de beleving van de niet-neuro-urologische patiënt binnen de verschillende domeinen van een functionele stoornis van de lage urinewegen en de bekkenbodem te evalueren zijn er verschillende Nederlandstalige PROMs beschikbaar. Bij de evaluatie van neuro-urologische patiënten worden conditie-specifieke vragenlijsten geadviseerd. Deze conditie-specifieke vragenlijsten zijn nog niet voor ieder domein in het Nederlands beschikbaar. In **hoofdstuk 6** is de Engelstalig Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-15) vertaald volgens standaard richtlijnen naar het Nederlands en zijn de meeteigenschappen geëvalueerd. De MSISQ-15 is een uit 15 vragen bestaande vragenlijst om symptomen van seksuele dysfunctie in patiënten met multiple sclerosis te evalueren. In deze studie werd de Nederlandse MSISQ-15 gevalideerd bij patiënten met multiple sclerosis of een ruggenmergaandoening (dwarslaesie of cauda equina syndroom). Bij inclusie vulden seksueel actieve patiënten met multiple sclerosis of een ruggenmergaandoening de Nederlandse MSISQ-15 in en als referentiemaat de Nederlandse Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) door vrouwen of de Nederlandse International Index of Erectile Function (IIEF-15) door mannen. Een tot twee weken later werden de vragenlijsten nogmaals ingevuld. Een controlegroep zonder neuro-urologische aandoening werd verzameld bij een huisartsenpraktijk, zij werden gevraagd de vragenlijst bundel eenmalig in te vullen. De testfase toonde een adequate content validiteit, de vragenlijst is duidelijk en omvat de problemen omtrent het seksueel functioneren bij een neuro-urologische aandoening. In de patiëntengroep was de MSISQ-15 score gecorreleerd aan de mate van seksueel disfunctioneren gemeten met de PISQ-12 of IIEF-15, wat wees op goede criteriumvaliditeit. De MSISQ-15 scores in de patiëntengroep (38.9 ± 11.4) waren hoger dan in de controlegroep (21.1 ± 5.4; $P < 0.001$), dit bevestigd een goede constructvaliditeit. De MSISQ-15 toonde goede interne consistentie (Cronbachs alfa

>0.8) en reproduceerbaarheid (intraclass correlatie coëfficënt >0.8). Deze studie toont aan dat de Nederlandse MSISQ-15 betrouwbaar en valide is om seksuele disfunctie in patiënten met MS of een ruggenmergaandoening te evalueren.

Een andere meeteigenschap van een vragenlijst is de responsiviteit. De responsiviteit van een vragenlijst geeft aan of de vragenlijst in staat is over de tijd klinische belangrijke veranderingen te detecteren. Er zijn twee Nederlandse gevalideerde vragenlijsten beschikbaar om functionele stoornissen van de lage urinewegen en bekkenbodem bij kinderen te kunnen evalueren: de Vancouver Symptom Score for Dysfunctional Elimination Syndrome (VSSDES) en Pediatric urinary incontinence Quality of life (PinQ). De VSSDES kan worden gebruikt om symptomen van dysfunctional voiding te evalueren. De PinQ evalueert de kwaliteit van leven bij kinderen met urine-incontinentie. Deze Nederlandse versies zijn valide en betrouwbaar. Echter was de responsiviteit van deze vragenlijsten, tot de studie in **hoofdstuk 7**, niet bekend. Deze studie toont aan dat de responsiviteit van de PinQ goed is in tegenstelling tot de responsiviteit van de VSSDES. Dit bevestigt dat de PinQ kan worden gebruikt in de evaluatie van de continentie-specifieke kwaliteit van leven bij de eerste presentatie, gedurende follow-up en na behandeling van een kind met dysfunctional voiding. Dit geldt niet voor de VSSDES. De VSSDES is een betrouwbare en valide vragenlijst om systematisch een objectief beeld te krijgen van de symptomen bij kinderen met dysfunctional voiding, zoals in eerder onderzoek is aangetoond. Het is een handig instrument naast de huidige diagnostiek (plasdagboek en uroflowmetrie met EMG van de bekkenbodem) voor de diagnosestelling dysfunctional voiding. Naast de responsiviteit, beschrijft de studie van **hoofdstuk 7** de uitkomsten van uitgebreide urotherapie bij kinderen met dysfunctional voiding op de symptomen van de lage urinewegen. Urotherapie is een niet-gestandaardiseerde conservatieve behandeling voor kinderen met plasproblemen. De behandeling bestaat uit de initiële evaluatie van symptomen, educatie en management. Uitgebreide urotherapie is urotherapie gecombineerd met visuele biofeedback door middel van een uroflowmetrie met EMG-elektrodes met of zonder training van de bekkenbodem. De meerderheid van de kinderen had na uitgebreide urotherapie een afname van 50% tot 100% van de lage urinewegen symptomen, ook wanneer de kinderen een eerdere onsuccesvolle behandeling hadden ondergaan.

Tenslotte, in de algemene discussie van dit proefschrift, **hoofdstuk 8**, wordt het valideren van PROMs en het analyseren van het behandelingseffect weergegeven door traditionele en patiënt gerapporteerde uitkomstmaten als toegevoegde waarde aan evidence based medicine bediscussieerd. De combinatie van evidence based medicine en shared decision-making dragen bij aan de optimalisatie van de klinische praktijk. Om behandelingsuitkomsten binnen de functionele urologie beter te kunnen vergelijken

is het nodig om consensus te bereiken over hoe de uitkomst zou moeten worden gedefinieerd. Er wordt een rol voor zowel een traditionele uitkomstmaat (objectief) als een PROM (subjectief) gesuggereerd. Als laatst worden de toekomstperspectieven van het standaardiseren van uitkomsten en de mogelijkheid tot een voorspelmodel in de functionele urologie besproken.

PART V

Appendices

LIST OF ABBREVIATIONS

ASA	American Society of Anesthesiologists
ASIA	American Spinal Injury Association
AUS	Artificial Urinary Sphincter
BNR	Bladder Neck Resection (chapter 2)
BNR	Bladder Neck Reconstruction (chapter 3)
BNS	Bladder Neck Sling
BOO	Bladder Outlet Obstruction
BOP	Bladder Outlet Procedures
BPH	Benign Prostate Hyperplasia
CVA	Cerebrovascular Accident
DV	Dysfunctional Voiding
EBC	Expected Bladder Capacity
EQ-VAS	EQ Visual-Analogue Scale
FU	Follow-up
IC	Intermittent Catheterization
ICC	Intraclass Correlation Coefficient
ICI	International Consultation on Incontinence
ICS	International Continence Society
ICCS	International Children's Continence Society
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
IPSS QOL	International Prostate Symptom Score Quality of Life item
IQR	Interquartile Range
LOA	Limits Of Agreement
LUT	Lower Urinary Tract
LUTS	Lower Urinary Tract Symptoms

MMC	Myelomeningocele
MS	Multiple Sclerosis
MSISQ	Multiple Sclerosis Intimacy and Sexuality Questionnaire
NLUTD	Neurogenic Lower Urinary Tract Dysfunction;
NR	Not Reported
NU	Neuro-urological
OR	Odds Ratio
PGI-I	Patient Global Impression of Improvement
PinQ	Pediatric urinary incontinence Quality of life score
PRO	Patient Reported Outcome
PROM	Patient Reported Outcome Measure
PPI	Post Prostatectomy urinary Incontinence
PISQ	Prolapse/Urinary Incontinence Sexual Questionnaire
RP	Radical Prostatectomy
RU	Residual Urine
SCI	Spinal Cord Injury
SD	Sexual Dysfunction
SPC	Suprapubic Catheter
SUI	Stress Urinary Incontinence
TUC	Transurethral Catheter
TURP	Transurethral Resection of the Prostate
UI	Urinary Incontinence
UTI	Urinary Tract Infection
VSSDES	Vancouver Symptom Score for Dysfunctional Elimination Syndrome

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- Noordhoff TC, Scheepe JR, Blok BFM. *Outcome and complications of adjustable continence therapy (ProACT) after radical prostatectomy: 10 years' experience in 143 patients.* Neurourol Urodyn. 2018 Apr;37(4):1419-1425. doi: 10.1002/nau.23463. Epub 2017 Dec 20.

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ABOUT THE AUTHOR

Toscane Noordhoff was born in Lisse, The Netherlands, on the 23rd of November, 1988. She attended high school at the Rijnlands Lyceum Sassenheim and graduated in 2007. After high school, she moved to Rotterdam to study Medicine. In August 2013 she obtained her medical degree cum laude at the Erasmus University in Rotterdam. Afterwards she started working as a "resident not in training" at the department of Urology of the Diakonessenhuis in Utrecht. From July 2014 until December 2015 she worked as a "resident not in training" at the department of Urology of the St. Antonius Ziekenhuis. In 2016 she started as a PhD student working on her thesis at the department of Urology at the Erasmus MC in Rotterdam (supervisors: Prof. dr. C.H. Bangma, dr. B.F.M. Blok, and dr. J.R. Scheepe). In the first year, she combined her PhD research with working as a "resident not in training" at the Pediatric Urology department of the Sophia Children's Hospital in Rotterdam. She worked fulltime on her research project to complete her PhD thesis in 2017 and 2018. During her PhD she coached four bachelor students Medicine, and she co-organized the Sophia Research Day in April 2018; a yearly symposium of the theme Erasmus MC-Sophia. In January 2019 Toscane visited the Academisch Ziekenhuis Paramaribo (AZP), Suriname, for an internship at the department of Urology. As of April 2019, she works as a "resident in training" at the department of General Surgery at the Ikazia Ziekenhuis in Rotterdam (supervisor: dr. P.T. den Hoed) as part of her residency in Urology. Toscane enjoys living together with Boudewijn Schuitmaker in Rotterdam.

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ERASMUS MC PHD PORTFOLIO

Name PhD student	Toscane Claudia Noordhoff
Erasmus MC department	Urology
PhD period	April 2016 – June 2019
Promotor	Prof. dr. C.H. Bangma
Supervisors	dr. B.F.M. Blok, dr. J.R. Scheepe

1. PhD training	Year	ECTS
General courses		
Research Integrity	2016	0.3
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2016	1.5
Basic Introduction Course on SPSS	2016	1.0
Endnote Course	2016	0.3
Biomedical English Writing	2017	2.0
Specific courses		
Summer Academy TIAS-MBE, August 2016, Tilburg, The Netherlands	2016	3.0
Seminars and workshops		
Department Journal Club	2016-2018	3.0
Department educational program 'refereeravond'	2016-2018	1.0
Department educational program 'onderwijsuur'	2016-2018	1.0
Presentations		
Oral presentation at the Sophia Research Day, Rotterdam, The Netherlands	2017	0.7
Poster presentation at the ICS meeting, Florence, Italy	2017	0.7
Oral presentation at the NVU, Nieuwegein, The Netherlands	2017	0.7
Oral presentation at the ICS meeting, Philadelphia, United States	2018	0.7
Oral presentation at the Erasmus MC 'refereeravond', Rotterdam, The Netherlands	2018	0.7
Oral presentation at the NVU, Nieuwegein, The Netherlands	2018	0.7
(Inter)national conferences		
32nd Annual EAU congress, London, United Kingdom	2017	1.0
NVU voorjaarsvergadering, Den Bosch, The Netherlands	2017	0.3
ICS meeting, Florence, Italy	2017	1.0
NVU Najaarsvergadering, Nieuwgein, The Netherlands	2017	0.3
33rd Annual EAU congress, Copenhagen, Denmark	2018	1.0
NVU voorjaarsvergadering, Nijmegen, The Netherlands	2018	0.3

1. PhD training	Year	ECTS
ICS meeting, Philadelphia, United States	2018	1.0
NVU Najaarsvergadering, Nieuwegein, The Netherlands	2018	0.3
Others		
Trial coordinator Artisan overactive bladder study (rechargeable neuromodulator)	2018	1.0
Organising committee Sophia Research Day 2018, Rotterdam, The Netherlands	2017-2018	3.0

2. Teaching	Year	ECTS
Lecturing		
Workshop 'PROMs in urology' at Multidisciplinary Symposium about Multiple Sclerosis, Nieuwegein, The Netherlands	2017	1.0
The course 'Urogenital trauma'	2017, 2018	1.0
The course 'Physical examination of men'	2018	1.0
Other		
Supervising interns at the paediatric urology clinic	2016	1.0
Coach of 4 bachelor medicine students	2017-2019	2.0

Total	32.5

Awards
Best in category prize 'paediatrics'
Oral presentation: Twenty-five years' experience in bladder outlet procedures in children with neurogenic urinary incontinence. ICS meeting 2018, Philadelphia, United States