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**URETHRAL STRICTURES IN MEN:  
STUDIES ON RECONSTRUCTIVE SURGERY AND  
PATHOPHYSIOLOGY**

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By

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Urethral Strictures In Men:  
Studies On Reconstructive Surgery And Pathophysiology  
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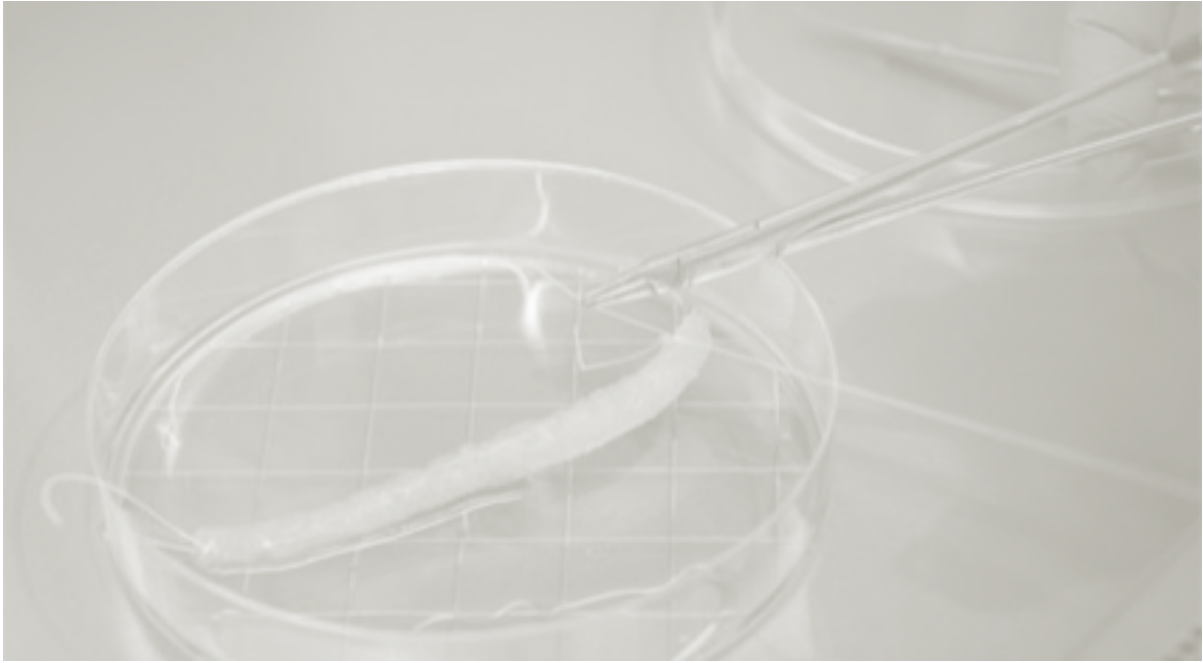
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To Iselinn, Kasper, Jonatan, and Fredrik

...the loves of my life.

“To the uneducated an A is just three sticks...”

Winnie-the-Pooh  
- A.A. Milne



# Urethral Strictures In Men: Studies On Reconstructive Surgery And Pathophysiology

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## ABSTRACT

Urethral stricture is a common disease that is characterised by fibrotic tissue arising from inflammation after urethral injury. Urination is inhibited when there is total obstruction, and the suffering is immense. Following the paradigm shift in treatments, from internal urethrotomy to open urethroplasty surgery, different surgical techniques have emerged. The aims of this thesis were to assess the outcomes of different reconstructive surgical techniques, including redo surgery, and to analyse the histopathology of urethral stricture disease.

All consecutive patients subjected to urethroplasty at Sahlgrenska University Hospital during the period 1999–2014 were identified and data were retrieved from their medical charts. Papers I-III were retrospective studies and Paper IV was prospective. All the patients were subjected to a follow-up regimen of 3, 12, and 24 months, and more if deemed necessary. If the patient was satisfied with his micturition after 2 years of follow-up, he was discharged from follow-up and instructed to come back if micturition problems should re-appear. Failure or re-stricture were in all the studies defined as the need for a new surgical intervention, such as dilatation, internal urethrotomy, or a redo urethroplasty. For bulbar strictures, treated with either transection with excision followed by anastomosis (EA) or using a graft as an onlay, **Paper I** reported success rates of 91% and 71%, respectively, with a low risk of sexual dysfunction. This indicates that EA is a feasible method for treating bulbar strictures.

In **Paper II**, penile strictures were studied; they were treated with one- and two-stage substitution urethroplasty, (SU) with success rates of 65% and 72%, respectively. Limited clinical experience, obesity and previous urethral surgery emerged as predictors for less favourable outcome.

In **Paper III**, 195 re-interventions performed for 82 failures out of 407 consecutive primary urethroplasties, were analysed. EA and SU were equally successful interventions for bulbar strictures. Twenty percent of the patients were cured with one single direct vision internal urethrotomy. After one or up to seven re-interventions in each patient, 18 patients remained as failures at the study end-point date, yielding an overall success rate of 78%. The most complex cases involved redo surgery for penile strictures, these complicated strictures probably need to be centralised at a specialised clinic, to ensure an optimal outcome.

**Paper IV** the histological findings of the resected part of the urethral stricture were analysed. The fibrosis was classified into Grades I–III, where III involved sclerosis. The occurrence of severe fibrosis with sclerosis was a strong predictor of failure after EA surgery for bulbar strictures.

*In summary*, transection and non-transection surgical procedures entail low rates of sexual dysfunction. Overall, bulbar strictures have a higher success rate than penile strictures, the latter being the most complex ones. Two-stage procedures, involving grafting of buccal mucosa, appear to be the most successful treatment for penile strictures. There are several risk factors associated with urethroplasty surgery. Redo surgery was a relatively rewarding treatment in this cohort, even though several re-interventions were needed to achieve a satisfactory outcome. Sclerosis is a risk factor for failure of urethroplasty in bulbar strictures. The establishment of a classification system for fibrosis paved the way for extended investigations into the origin how strictures develop on the cellular level, as well as novel therapeutic regimens.

*Keywords:* urethral stricture; transection; urethroplasty; sexual dysfunction; sclerosis; fibrosis; obesity; redo surgery

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## LIST OF PAPERS

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

- I. Teresa O. Ekerhult, Klas Lindqvist, Ralph Peeker and Lars Grenabo. **Low risk of sexual dysfunction after transection and nontransection urethroplasty for bulbar urethral stricture.**  
J Urol. 2013; 190: 635-8.
- II. Teresa O Ekerhult, Klas Lindqvist, Ralph Peeker and Lars Grenabo. **Limited experience, high body mass index and previous urethral surgery are risk factors for failure in open urethroplasty due to penile strictures.**  
Scand J Urol. 2015; 49: 415-8.
- III. Teresa O Ekerhult, Klas Lindqvist, Ralph Peeker and Lars Grenabo. 2016. **Outcomes of re-intervention after failed urethroplasty.**  
Submitted for publication in Scandinavian Journal of Urology.
- IV. Teresa O Ekerhult, Klas Lindqvist, Lars Grenabo, Christina Kåbjörn and Ralph Peeker. 2016. **Sclerosis and severe fibrosis as a predictive factor for restructure after bulbar urethroplasty.**  
In manuscript.

## ABBREVIATIONS IN ALPHABETICAL ORDER

BM	Buccal mucosa
BMI	Body mass index
BXO	Balanitis xerotica obliterans
CISD	Clean intermittent self-dilatation
DVIU	Direct vision internal urethrotomy
EA	Excision/transection with anastomosis
ED	Erectile dysfunction
FG	Fibrosis grade
LS	Lichen sclerosus
PU	Perineal urethrostomy
SL	Stricture length
SU	Substitution urethroplasty-onlay/inlay
SU:1	One stage substitution urethroplasty
SU:2	Two stage substitution urethroplasty
TGF- $\beta$ 1	Transformal growth factor- $\beta$ 1

## SHORT OVERVIEW OF PAPERS

Paper	Design	Endpoints	Main findings
<b>I</b>	<ul style="list-style-type: none"> <li>*Retrospective chart study of <b>bulbar strictures</b>, 161 patients (169 procedures)</li> <li>*1999–2009</li> <li>*EA, N=94</li> <li>*SU:1, N=75</li> </ul>	<ul style="list-style-type: none"> <li>*Assess sexual function after urethroplasty</li> <li>*Outcomes of EA and SU:1 treatments</li> </ul>	<ul style="list-style-type: none"> <li>*Low risk for sexual dysfunction after both EA and SU:1.</li> <li>*EA success rate of 91%</li> <li>*SU:1 success rate of 71 %</li> </ul>
<b>II</b>	<ul style="list-style-type: none"> <li>*Retrospective chart study of <b>penile strictures</b>, 90 patients (109 procedures)</li> <li>*2000–2011</li> <li>*SU:1, N=80</li> <li>*SU:2, N=29</li> </ul>	<ul style="list-style-type: none"> <li>*Assess possible risk factors for failure</li> <li>* Surgical outcomes of SU:1 and SU:2</li> </ul>	<ul style="list-style-type: none"> <li>*Limited clinical experience, BMI&gt;30 and previous urethral surgery were risk factors for failure</li> <li>*SU:1 success rate of 65%</li> <li>*SU:2 success rate of 72%</li> </ul>
<b>III</b>	<ul style="list-style-type: none"> <li>*Retrospective chart study of 82 failed urethroplasties, 26 <b>penile strictures</b> and 56 <b>bulbar strictures</b></li> <li>*1999–2013</li> <li>*Total reinterventions, N=195</li> </ul>	<ul style="list-style-type: none"> <li>*Assess the outcomes of patients with failed urethroplasties at a single tertiary referral center</li> </ul>	<ul style="list-style-type: none"> <li>*Redo surgery was slightly more successful if previous EA was performed as a primary urethroplasty.</li> <li>*EA and SU were equally successful as reintervention for bulbar stricture.</li> <li>*A single DVIU was a good first treatment for early and short bulbar stricture recurrence.</li> <li>*Penile stricture redo surgery represented the most complex cases.</li> </ul>
<b>IV</b>	<ul style="list-style-type: none"> <li>*Prospective histological study of <b>bulbar strictures</b>, 45 consecutively patients</li> <li>*2011–2014</li> <li>*EA, N=45</li> <li>*Histological examination of bulbar stricture specimens by an uropathologist blinded to the original diagnosis, as well to the study design.</li> </ul>	<ul style="list-style-type: none"> <li>*To describe and categorise the fibrosis</li> <li>* The primary aim was to disclose whether or not the degree of fibrosis is a predictive factor for the outcome after open urethroplasty.</li> </ul>	<ul style="list-style-type: none"> <li>*Severe fibrosis with sclerosis came out as a predictive risk factor for resticture after EA.</li> <li>*Inflammation did not emerge as risk factor for failure.</li> </ul>



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## INTRODUCTION AND HISTORICAL BACKGROUND

### General History

Urethral stricture is a common disease that has been known for a long time. Considering that dilatation was described before 600 BC, treatment of urethral strictures is one of the oldest medical interventions (1). Urethral dilators, comprising various materials (such as metal, wood, papyrus and feathers), have been found in the tombs of the Pharaohs. In ancient times people knew that having a stricture meant having it for life and that the only possible remedies were both short-term and risky.

In addition, over thousand years ago, there are descriptions in the literature of not only dilatation being performed, but also internal urethral incision and external urethrotomy. Typically, an incision was made in the perineum, aiming towards the bulbar urethra. Massive bleeding and infection presumably occurred frequently, and one can imagine that the survival rate was not high. In a more recent century, Fisher and Ravasisni 1937 applied the technique of visual internal urethrotomy. This procedure started to be applied more widely when, in 1971, Sachse described direct visual internal urethrotomy, although he was not alone in recognizing the benefit of this fantastic tool.

An alternative treatment is open urethroplasty. Surgical reconstructive surgery for urethral strictures started with resection with end-to-end anastomosis, as reported by Rochet (1899), Guyon (1892), and Russell (1914), before internal urethrotomy, albeit with unacceptable results. Two principles are applied in urethroplasty surgery that we indisputably perform today; 1) the need for spatulation at the anastomosis; and 2) tension-free anastomosis with proper mobilisation of the urethra, which they in old times overlooked. Compared to previous eras, the surgical equipment used and anaesthesia has improved enormously, with better sutures, catheters, antibiotics, and rigorous clinical routines, so of course it was a challenge for them to succeed.

One of the pioneers of two-stage operations was Bengt Johanson (2, 3), who applied a new technique that he described in his thesis in 1953 (4). His idea was to use the flexibility of the scrotal skin to operate on bulbar urethral strictures up to the membranous part. Hans Marberger (5, 6), and his co-workers at Innsbruck introduced the Johanson-procedure to the field of urology and made this method well known. Nevertheless, this operation was hampered by poor long-term results, such as the appearance of pseudo-diverticula and abscesses due to the fact that the urethra was reconstructed with hair-bearing scrotal skin.

In 1957, Pressman and Greenberg described the full-thickness skin graft patch urethroplasty technique. Subsequently, Devine published a series of papers describing improvements to and expansion of this technique.

Later on in 1970, Schreiter (7, 8) described a two-stage mesh graft operation, whereby several of the disadvantages of the Johanson technique were eliminated. This procedure was also used for longer and more complex recurrent strictures.

Moving on to 1975, Turner-Warwick (9, 10) reported excellent results with the application of an oblique end-to-end anastomosis to the bulbous region of the urethra (Fig. 1). Based on these achievements, further developments were possible. Resection of the stricture in combination with primary end-to-end anastomosis became a routine procedure in many

urological institutions around the world as improved long-term results were obtained.

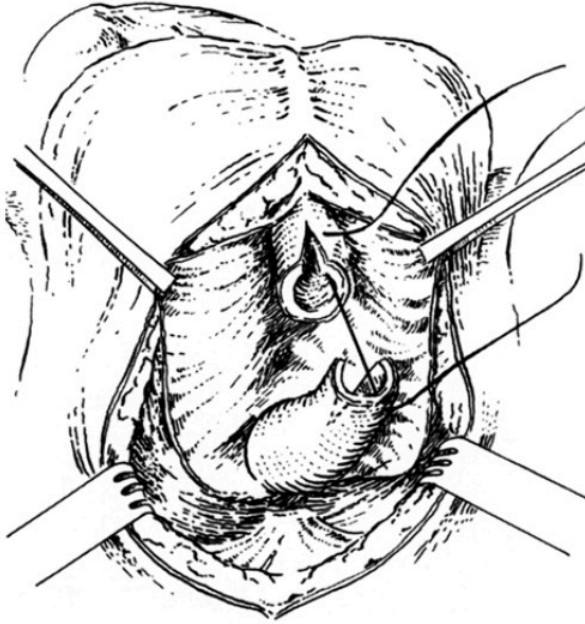
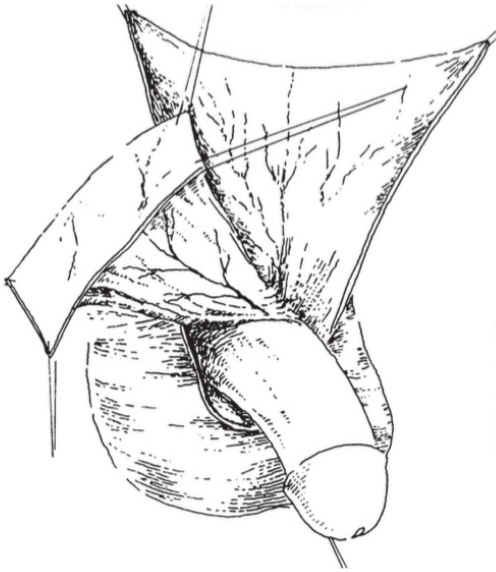


Figure 1. Oblique end-to-end anastomosis. (Courtesy of Operative Therapie der Harnröhrenstriktur, von Klaus Bandhauer und Friedhelm Schreiter, 1991, Georg Thieme Verlag, Stuttgart, New York)

From the time of its description to the early 1980s, full-thickness skin patch graft urethral reconstruction became the standard for single-stage urethral reconstruction for addressing strictures. However, the early success rates in the mid-80 % range were never exceeded, and long-term follow-up showed deterioration and left much to be desired. Duckett introduced the transverse preputial island flap technique in 1980, a method that enabled the repair of long stretches of the urethra in a single surgical session (Figure 2.).



Figur 2. Duckett's pediculated transversal preputial island flap, used to repair long stretches of urethra. (Courtesy of Operative Therapie der Harnröhrenstriktur, von Klaus Bandhauer und Friedhelm Schreiter, 1991, Georg Thieme Verlag, Stuttgart, New York)

There was a paradigm shift from foreskin to buccal mucosa for the use in substitution urethroplasty during early 90's. However, more than hundred years ago, Dr Kirill Sapezhko from Russia presented his thesis "Clinical material to the topic of mucosal transposition" at the 11<sup>th</sup> International Medical Congress in Rome in 1894 (De Historia Urologiae Europaeae, volume 19, Prof. Dr. Dirk Schultheiss, EAU, 2012). It was very prescient of Sapezhko at the end of the 19<sup>th</sup> Century to recommend oral mucosa graft transplantation in plastic urethral surgery, as hundred years later it become a widely adopted and promising method. However, thanks to the Mainz school of Urology, Bürger and colleagues reported in 1992 the first results of animal experiments, in which the oral mucosa was used for reconstruction of the urethra (11). Based on these findings, oral mucosal grafts were used not only to replace the urethra in cases of hypospadias injuries, but also for the operative treatment of urethral strictures.

In recent times, there has been a resurgence of interest in graft techniques, particularly with the advent of buccal mucosal grafting. Island flap techniques are still applicable, although their use has drastically diminished. Currently, the buccal mucosal grafting method predominates. For the treatment of strictures associated with lichen sclerosus, it is considered the method of choice. The staged mesh graft operation is retained for very complex situations, e.g. when the available penile skin is insufficient or the buccal mucosa donor site is not adequate for the degree of stricture. Tissue engineering is by many considered by many to be the future of urethral reconstruction. Repair of urethral strictures has changed in a radical way, with several paradigm shifts having occurred over the last century. In the past, one had temporal treatments, whereas today our aim is to cure our patients. This brief piecemeal history summarises the development of reconstructive surgical treatments for urethral disorders, which have continuously improved over the past decades.

## Experience from The Sahlgrenska University Hospital

At Sahlgrenska University Hospital, there is a long-standing interest in urethral strictures, starting with the invention by Bengt Johansson of the scrotal two-stage procedure described above. Björn Asklin presented his thesis in 1983 on “Evaluation of infravesical obstruction and endoscopic treatment of the urethral stricture”. In one of the papers in his thesis, he analysed the length of catheter-time after internal urethrotomy, where eight days and five weeks showed only minor differences in success rate, 50% and 60%, respectively (12). Silas Pettersson, also analysed the outcomes of endourethral urethroplasty in a pilot study with nine patients, in which six grafts survived and only three of the patients were recurrence-free after over five years of follow-up (13).

The story of the present thesis commenced in the mid- 90’s, when Lars Grenabo started to perform urethroplasties. Shortly thereafter, Klas Lindqvist joined Lars to perform all open urethroplasty surgery. Initially, the majority of the urethral strictures were treated according to the Orandi technique, with a fasciocutaneous flap using penile skin for the penile strictures and free penile skin grafts for the bulbar strictures. In 2005, there was a shift towards excision with anastomosis. During this period, the buccal mucosa was introduced as a novel graft tissue.

The cohort in the present thesis comprised all consecutive patients who were operated on from the start of 1998 to the present day. The thesis is a descriptive analysis of the complexity of urethroplasties in a clinic that was started from scratch. With time the surgeons gained experience and our clinic has evolved into an urethroplasty centre. In 2006 my interest in these procedures was awakened, which led to a doctoral student application in 2007 and the book you hold in your hand is the result.

# ANATOMY AND PATHOPHYSIOLOGY OF THE URETHRA

## Anatomy

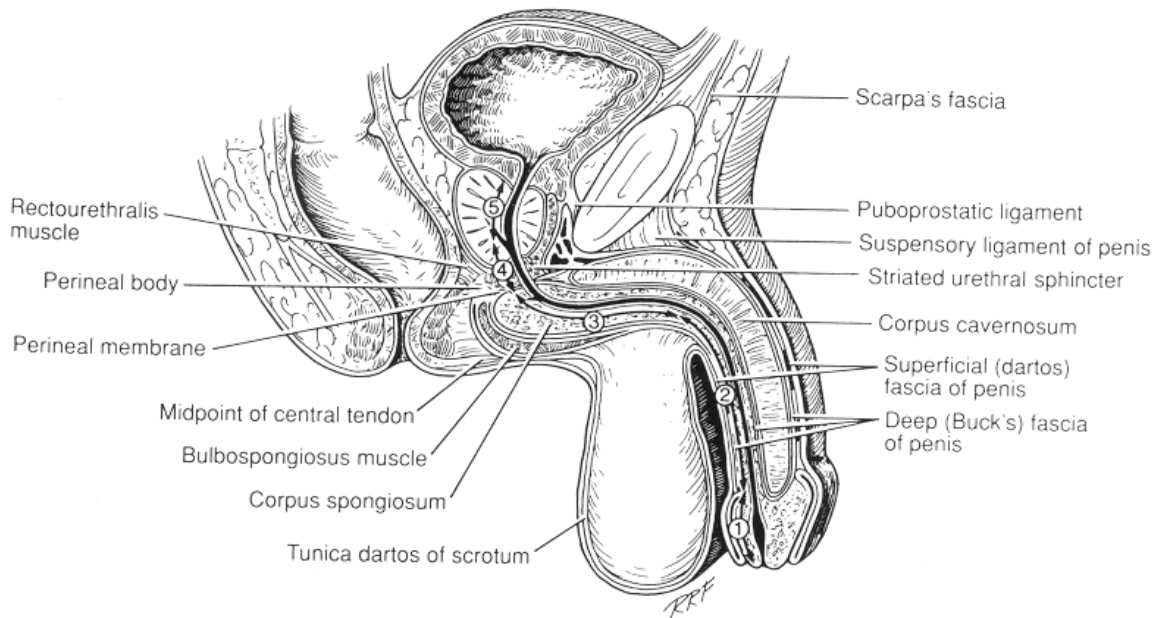


Figure 3. The anatomical regions of the urethral structures are the: 1) meatus with fossa navicularis; 2) penile urethra; 3) bulbar urethra; 4) membranous urethra; and 5) prostatic urethra.

The urethra may be divided into the anterior and the posterior parts according to various published literatures. The anterior part includes the fossa navicularis, penile and bulbar urethra. The posterior part includes the membranous and the prostatic urethra. In our series we do not use the nomenclature of anterior or posterior to define localisations for strictures. Instead, we use the names of the different parts of the urethra; meatus with fossa navicularis, penile, bulbar, membranous and prostatic urethra (Figure 3.).

Urethral epithelium changes from urothelial transitional cells to pseudostratified or stratified columnar epithelium after the membranous urethra, which extending to the fossa navicularis that has a stratified non-keratinising squamous epithelium (14). The lamina propria of the penile urethra is a fibroconnective tissue that contains elastic fibres and scattered, longitudinally oriented smooth muscle.

The length of the penile urethra is a matter of some discussion, with some investigators claiming that it is about 15 cm and extends from where the bulbospongiosus muscle ends to the tip of the glans penis at the urethral meatus, whereas others have estimated the pendular penis as having a mean length of 9,1 cm (15). The bulbar part of the urethra is about 3–4 cm in length and has a larger luminal calibre than the urethra in the prostatic or membranous part.

The most proximal part of the urethra comprises the membranous part of the urethra (2–2,5 cm), the shortest segment of the male urethra, and the prostatic urethra (3-4 cm). (Figure 3.) The skeletal muscle fibres of the urogenital diaphragm surround the membranous part, which is a part of the external urethral sphincter.

The penile urethra is surrounded by the corpus spongiosum in its entire length. The following explains the layers that surround the structures of the penile shaft (Figure 4.); the corpora cavernosa are two bodies that are fused but partly separated by a septum attached to the surrounding tunica albuginea, ventrally and dorsally. Buck's fascia surrounds the tunica albuginea, containing the dorsal neurovascular structures and on the ventral side surrounding the corpus spongiosum, where the dorsal part of the corpus spongiosum is attached to the tunica of the corpus cavernosum. On the outside of Buck's fascia a loose surrounding layer of Dartos fascia is found, containing the superficial neurovascular structures, ending with a last layer of skin.

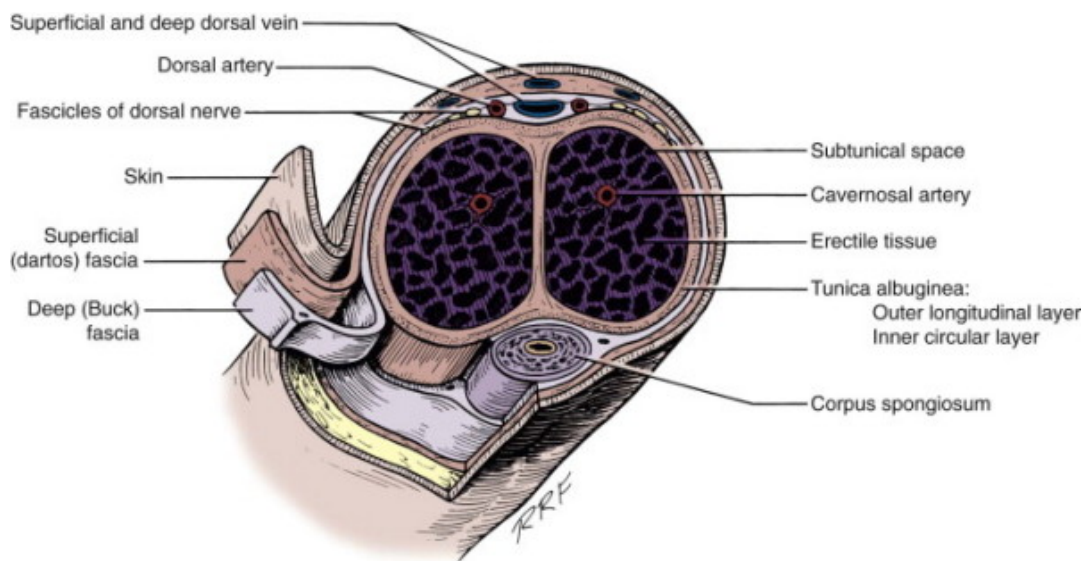


Figure 4. The fascia layers illustrated in a cross-section of the penis.



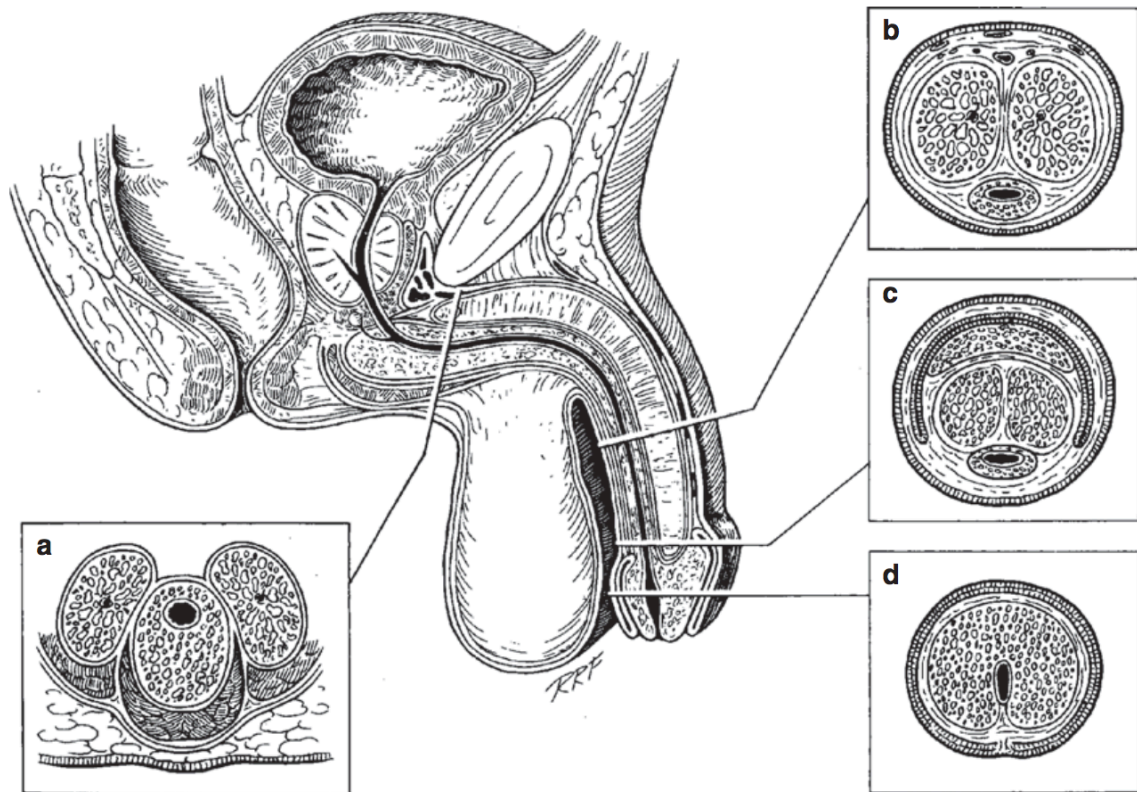


Figure 5. Cross-sections of the urethra in different parts of the penis; (a) at the bulbous urethra. (b) at the penile shaft; (c) at the coronal margin; (d) at the glans. (Jordan GH. Complications of interventional techniques for urethral stricture. In: Carson CC, editor. Complications of interventional techniques. New York: Igaku-Shoim; 1996. p. 89.)

### Vascular supply

The urethra has the unique vascular feature of having a dual blood supply, which is the reason why it can be mobilised extensively and divided. Separate arterial blood supplies feed the proximal and distal ends of the urethra. The common penile artery, which is a branch of the internal pudendal artery, first branches into the bulbar and circumflex cavernosal arteries (supplying the proximal corpus spongiosum) and then bifurcates into the central cavernosal arteries and into the dorsal artery of the penis. The dorsal artery arborises and penetrates into the glans penis and then flows in a retrograde fashion into the spongiosum. Thus, the corpus spongiosum has two blood supplies; proximally, the bulbar and circumflex arteries; and distally, branches of the dorsal penile artery (Figure 6.). The venous drainage of the corpus spongiosum comprises the venous drainage of the glans penis and the other deep structures, occurring via the periurethral veins, the circumflex veins, and the deep and superficial dorsal veins.

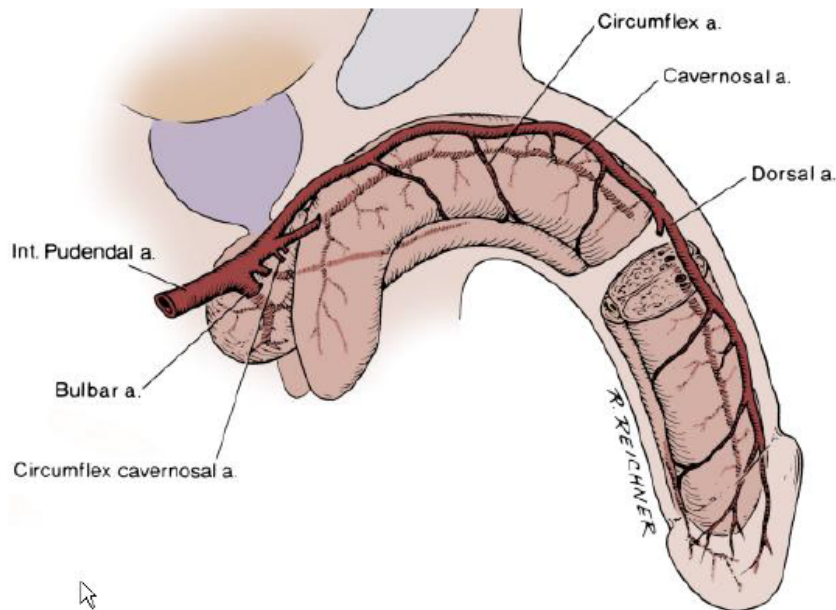


Figure 6. Urethral and penile arterial blood supplies. According to Jordan et al.(16)

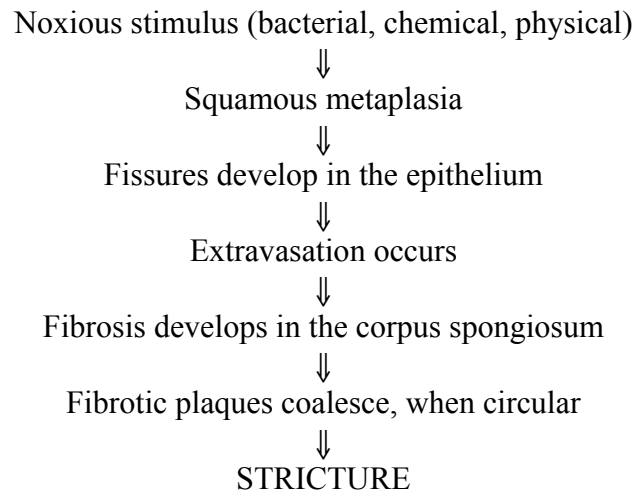
### Innervation

The pudendal nerve, which is the main nerve serving the male genitalia divides into three branches: the perineal nerve (17); the dorsal nerve of penis; and the inferior rectal nerve. The bulbospongiosus and ischiocavernosus muscles derive their motor supply from the perineal nerve, which innervates the structures in the pelvic floor. One study has highlighted the role of the perineal nerve in bulbospongiosus muscle contraction, where ejaculatory disturbances may arise due to the interruption of reflex pathways that provide innervations to the bulbospongiosus muscle (18). Such disorders are manifested as decreased force of semen expulsion and possible sequestration of urine and semen in the bulbar urethra. The perineal nerve, in the form of the fine branches extending to the corpora spongiosa, can be damaged during retraction of the incised muscle or during dissection of the central tendon of the perineum. Resuturing of the muscle at the midline does not necessarily restore muscle function to the baseline level, as there is still damage to the nerve fibres. Muscle- and nerve-sparing ventral and dorsal onlay bulbar urethroplasty first described in 2008 and subsequently combined with SU using buccal mucosa, has reduced the incidence of stricture recurrence and frequency of postoperatively complications (19, 20).

### Pathophysiology

The characteristic feature of a stricture is fibrous tissue replacing the corpus spongiosum deep under the urethral epithelium. Only a few studies have been conducted on the pathogenesis of the stricture disease, primarily using animal models (14, 21-23). The primary change observed in stricture is metaplasia of the urethral epithelium from normal pseudostratified columnar to stratified squamous epithelium (24), which is more fragile and tends to split when inflated during bladder emptying. The created fissures, ulcers and regions of inflammations cause extravasations of urine leading to sub-epithelial fibrosis. These foci of fibrosis coalesce over a period of years to form macroscopic plaques that may eventually obliterate the urethra. There

is still some controversy whether the fibrosis present in strictures varies from the fibrosis that occurs in wound healing (25, 26).



A series of processes injuring the urethra or the corpus spongiosum to the degree that the healing promotes fibrosis and scar tissue formation, which results in a urethral stricture. Currently, we do not have a grading scale for fibrosis. Such scale would be useful for examining a potential correlation between the grade of fibrosis and restructure, which to our knowledge has not been investigated yet.

## INCIDENCE AND PREVALENCE

The exact current prevalence of urethral strictures of today is actually unknown and can only be gathered from population-based datasets, the quality of which varies throughout the world. Stricture prevalence is thought to be much higher in non-industrialised countries than in industrialised. Based on epidemiological data, the United States is estimated to have a prevalence of 0.9% (27). Symptomatic strictures that require treatment is the best indicators we have of exactly how common strictures really are, and these are easily identified from hospital admission data. The Hospital Episode Statistics (HES) unit analysed the data in the UK Department of Health database, which indicated that on average a hospital urology department that serves a population of half a million expects to see each year about 115 symptomatic patients who are deemed to require urethrotomy or dilatation based on currently accepted indications. In comparison, only about six or seven patients from that same population will require urethroplasty, again using current indications (28). The incidence in the 21st century in the UK' department of health >16 000 men require admission to hospital each year because of urethral stricture disease and >12 000 of them need an operation at an annual cost of ≈£10 million (29). The estimated prevalences in the UK is about 10/100 000 men in their youth rising to about 20/100 000 for mean age 55 years and 40/100 000 by the age of 65 years and to over 100/100 000 for men over 65 years (30). In our cohort, the mean age is 46 years and age range is 16–85 years old (Figure 7). Nowadays, the patients who suffer from urethral stricture are generally younger than before, mainly because they are treated directly without having undergone years of dilatations and DVIU, which may be the reason for the discrepancy between our cohort and other patient series (30, 31). Even higher rates of urethral stricture have been reported from the USA (31). Urethral strictures are uncommon in children, although they may appear after surgery for hypospadias and even having hypospadias may induce urethral stricture disease. Strictures are rarely found in women, but not unknown (32).

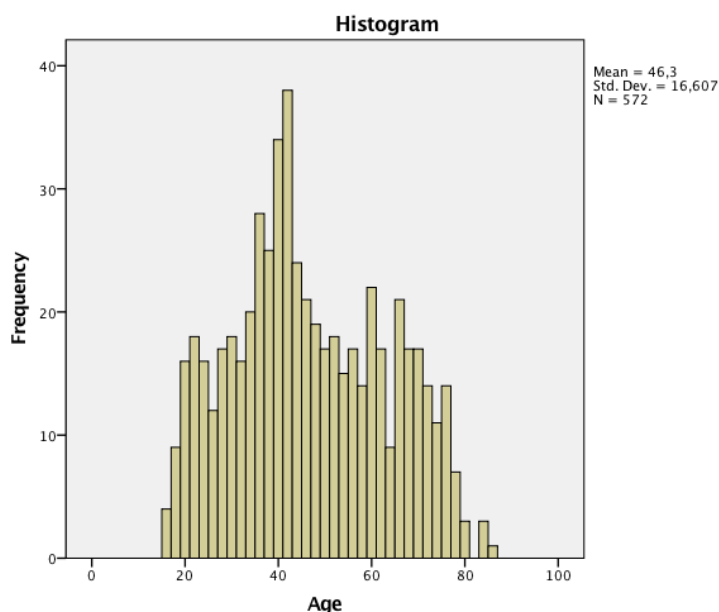


Figure 7. Age distribution profile (mean 46 years; range 16–85 years) of the cohort of patients (n=572) who underwent urethroplasty surgery in the period of 1998–2013 at Sahlgrenska University Hospital, Gothenburg, Sweden.

## AETIOLOGY OF URETHRAL STRICTURES

### Infection and inflammation

In the previous century gonorrhoea has been associated with stricture disease, however less common today. Because of the small paraurethral glands of Littre, greatest concentration is in the bulbar urethra, where abscesses may develop due to infection and in turn stricture formation occurs. This is why a relatively short stricture can ascend or descend when slowly progression may occur. Infected urine can also extravasate into the corpus spongiosum and result in spongiofibrosis. Long fibrotic strictures may also originate from tuberculous prostatitis, more common in undeveloped countries. Moreover, there are inflammatory strictures associated with balanitis xerotica obliterans, which is the same as lichen sclerosus, presented below.

### Lichen sclerosus

There is a clear association between the development of an inflammatory stricture and lichen sclerosus (LS), also known as balanitis xerotica obliterans (BXO). This is a chronic inflammatory disorder of the skin with unknown aetiology. In Latin, *sclerosus* means “a hardness, hard tumour” and in Greek, *sklerosis* means “hardening”. LS begins as inflammation of the prepuce, which may cause phimosis, although it can also appear on the glans as a white plaque and ascend into the urethra as well and lead to meatal stenosis. The pathophysiology of LS is poorly understood, although suggestions have been put forward that it might be an autoimmune phenomenon with a genetic component (33). Other possible aetiologies that have been proposed for LS include the Koebner phenomenon (34), oxidative stress, and infection. It can cause a sclerotic hard white ring, creating a phimosis. It is not clear whether LS spreads by direct extension into the penile urethra or if urethral involvement is secondary to LS-induced meatal stenosis and subsequent inflammation of the glands of Littre. The classic radiographical appearance of the LS-induced anterior urethral stricture is a saw-toothed pattern. While the German dermatologist Stümer hypothesised in 1928 that LS was caused by exposure of the glans after circumcision, this seems unlikely given that LS has also been found in uncircumcised males. The incidence in the Western world is under-reported. Based on ethnicity, the frequencies of LS diagnoses per 100,000 visits in the US are reported as: 2.1 for Caucasian; 0.9 for Asian and 1.4 in African American (35). In men, LS peaks between the ages of 30 and 60 years (Figure 8.). While both genders can be affected, although genital involvement is much more common in women.

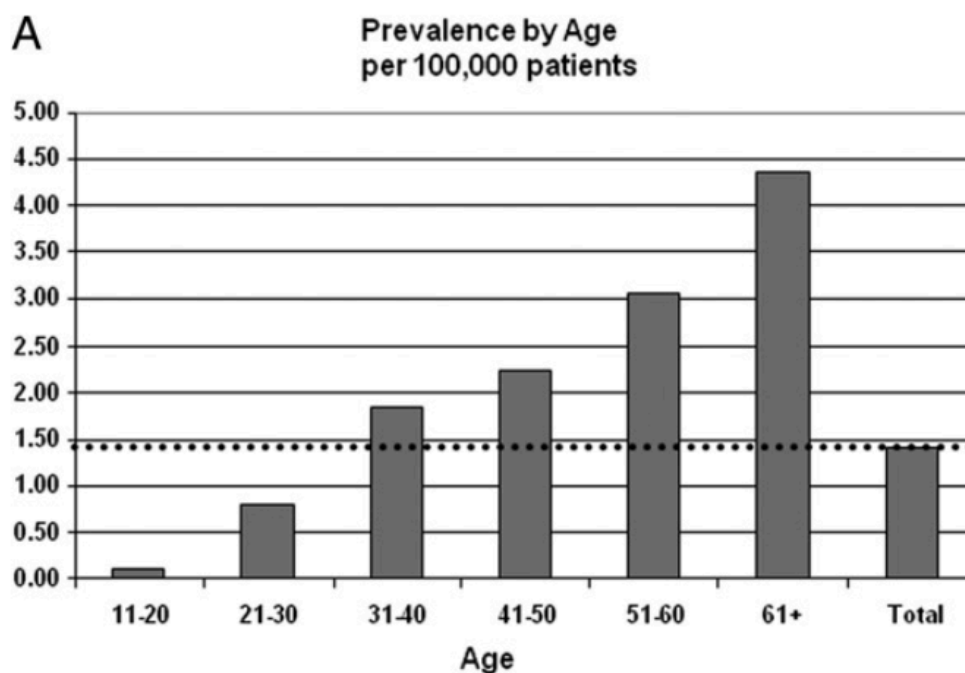


Figure 8. Age distribution of men with LS. The dotted line indicates the overall number of men, diagnosed per 100,000 patients (35).

### Previous surgery for congenital hypospadias

The incidence of hypospadias in new-born males is 1 in 300, which makes this the most frequent anomaly of the male genitalia (36). The meatal position of the hypospadias is most commonly in the coronal sulcus of the penis (70% of cases), and is equally disposed over the penile shaft. Patients with juvenile hypospadias often have problem with urethral stricture in adulthood; even more when previous surgery for hypospadias has been performed.

### Traumatic

Many of the urethral strictures are results after trauma, which in most cases are an iatrogenic trauma in connection with urethral instrumentation, such as transurethral surgery and during catheterisation. Another common trauma is the straddle injury, when falling of a bike or over a roof baulk, traumatising direct onto the perineum. Severe pelvic fracture may cause a urethral rupture followed by dense fibrotic strictures. In these cases the cardinal symptom is blood from the meatus. In the emergency room a suprapubic catheter is positioned and the reconstruction is performed after 3-4 months normally. When minor traumas occur, the patients are often unaware of their stricture until aberrant voiding symptoms appear.

### Idiopathic

When the cause of the stricture is unknown it is called an 'idiopathic stricture', which is the most common cause according to the literature (37, 38).

## DIAGNOSIS

Patient discomfort often starts with voiding problems, such as increased micturition time, a feeling of incomplete bladder emptying, dribbling, and a prolonged and weak flow, all of which can lead to urinary retention (Figure 9).

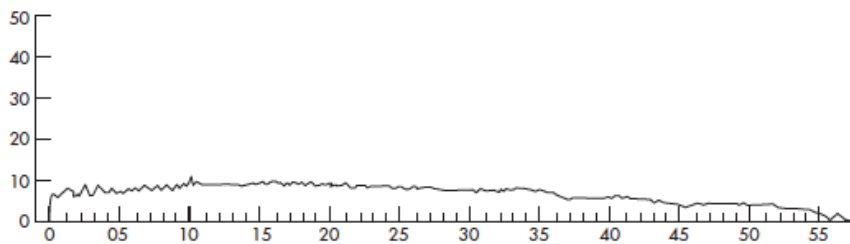


Figure 1 Flow pattern of a patient with a urethral stricture.

Figure 9. Flow pattern of patient with urethral stricture. (Review article Urethral stricture by AR Mundy and D Andrich: BJUI: 107;6-26.)

To decide on an appropriate treatment plan, it is important to determine the stricture location and length, which requires a flexible or rigid cystoscopy, or in the case of severely obstructed strictures, a ureteroscopy. When needed imaging studies are performed. Retrograde urethrography (RUG) and voiding cystourethrography (VCUG) are the most commonly employed methods for imaging of the male urethra. Conventional urethrography is performed under fluoroscopy with the hip tilted and the penis slightly stretched. In inadequate oblique images, the “true” stricture length will be underestimated and the pubic bones may obscure the urethra. VCUG is most valuable for assessing the urethra, the proximal extent of stenoses, and their functional significance. (Figure 10.)

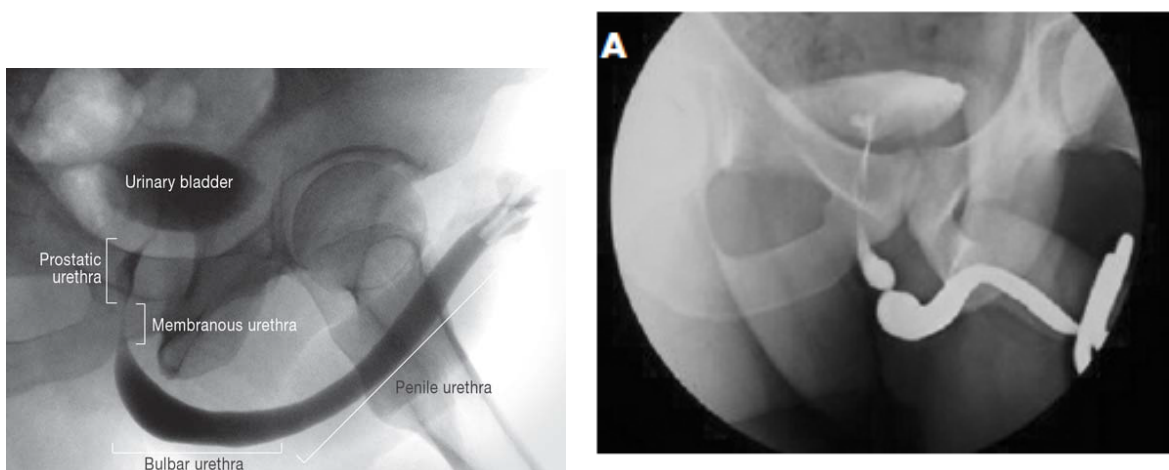


Figure 10. Voiding cystourethrograms of a normal urethra (left) and a short bulbar stricture (right).

Other modalities, such as CT, MRI and sonourethrography, have important albeit limited roles in urethral evaluations. MRI and CT have particular value in evaluating the patient who has a pelvic fracture with associated urethral disruption injury. Sonourethrography (Figure 11.) can be used to determine the true length of a bulbar urethral stricture and the extent of luminal narrowing.

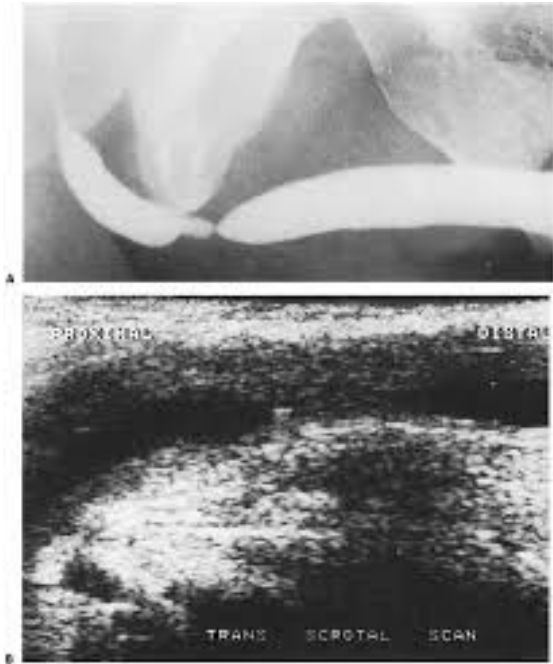


Figure 11. Sonography of the urethra.



## ENDUROLOGICAL TREATMENTS

### Dilatation

Dilatation is the oldest and simplest treatment for urethral stricture disease. The procedure intends to stretch the scar without producing additional scarring, which occurs if there is bleeding during the dilatation. This may be achieved using metal dilators or gradually progressive serial soft catheter dilatations at the hospital at intervals of some months, and can also be performed by the patients themselves using clean intermittent self-dilatation (CISD) at various intervals. (Figure 12.) However, one must bear in mind that this is often a life-long treatment, which is acceptable by some patients. Several decades ago dilatations were commonly performed at our outpatient urology clinics but this is not the case today, as more definitive treatments options are available.

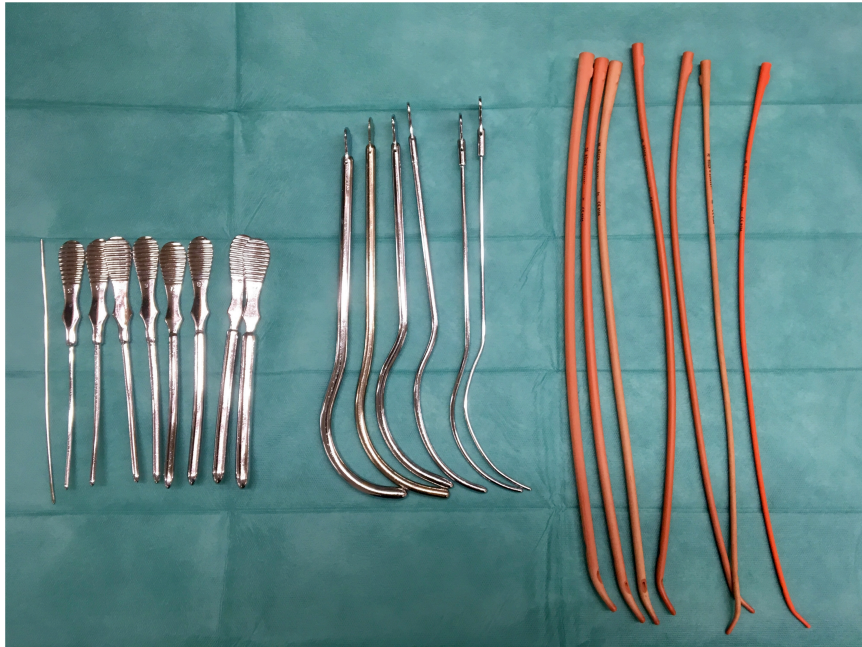


Figure 12. Hegar dilators, Gyons sounds and dilatation catheters (red) in different sizes are shown from left to right.

### Internal urethrotomy

Direct vision internal urethrotomy (DVIU), which is a minimal invasive intervention, involves an endoluminal cold knife incision through the scar of the stricture, often at the 12 O'clock position into healthy tissue, to widen the lumen and allow the cystoscope to pass through. (Figure 13.) Most reports on DVIU describe a 12 O'clock simple incision, which may minimise the risk of severe haemorrhage due to inadvertent incision of the corpus cavernosum (39-42).

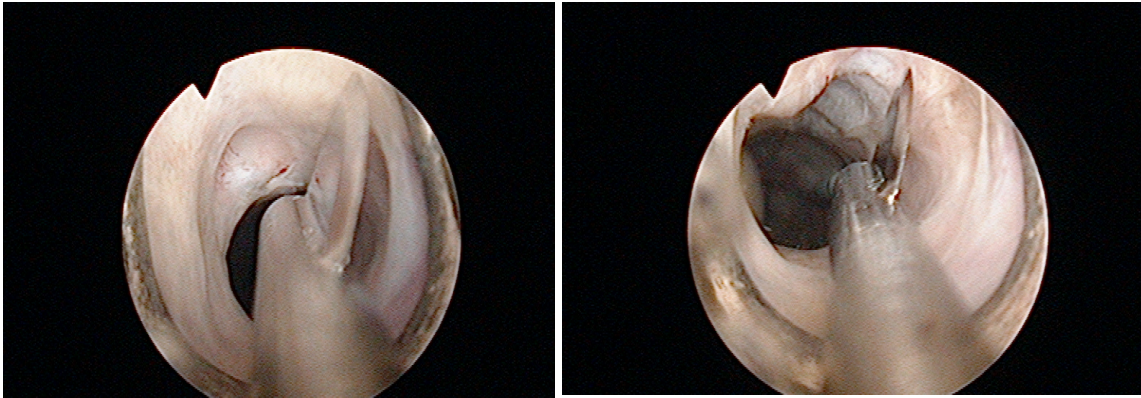


Figure 13. Direct vision internal urethrotomy.

If the surgeon is experienced and the stricture is short, incision with a guidewire is not necessary. If it is difficult to visualise the stricture lumen it is often useful to introduce a safety guide wire over which the stricture can then be incised. A silicon catheter is usually inserted after DVIU, often for some days to prevent bleeding. The success of the procedure usually depends on the aetiology of the stricture, as well as the length and the location. The success rate of DVIU for short strictures is high, at about 71–84% if the stricture is less than 1 cm, with longer and multiple strictures yielding a success rate of 35–54% (43). Patients with inflammation and pelvic trauma have poorer outcomes than patients with strictures that are due to urethral manipulation (44). Advanced age, obesity and idiopathic aetiology may be independent predictors for failure after DVIU (45). Antibiotic prophylaxis reduces stricture recurrence (46, 47). A lower recurrence rate has been reported for bulbar strictures than for penile strictures that might be explained by the thicker tissue and greater vascularization of the proximal urethra (39, 40, 48-52). In addition, the recurrence rate is lower for single strictures than for multiple strictures (53, 54). Most stricture recurrence occurs within 3–12 months after DVIU, according to the literature, while the risk of recurrence diminishes after 12 months (39, 41, 47). Even though 10 years of follow-up are recommended when resticture can occur up to 8 years after DVIU (50), far from all follow this recommendation.

## OPEN URETHROPLASTY

### Substitution urethroplasty (SU)

SU means that a transplant being placed in the stricture area, from outside (onlay) or from inside (inlay), to increase the urethral lumen. The transplants can be pediculated flaps in one-stage substitution urethroplasty (SU:1) and free grafts in either one stage (SU:1) or two stage procedure (SU:2). Various options exist for the surgical technique to be used for SU and the selection of repair method depends on the aetiology and the characteristics of the stricture, penile tissue quality, as well as on the surgeons' experience and the patient's expectations. A flap consists of tissue that is transferred together with its own blood supply and it requires a preserved and well-vascularised pedicle. A penile skin flap used as a pediculated flap can provide a superb option for repairing strictures of various locations and lengths. In this instance, it is important that the penile skin is healthy, without lichen sclerosus (LS). Patients with a peripheral vascular disease, diabetes or a history of smoking, all of which compromise blood flow, may experience high skin flap failure rates. Therefore, it is of importance to consider patient comorbidities before urethroplasty surgery. Free grafting using penile skin or buccal mucosa is used for both penile and bulbar strictures. When LS is present in the penile strictures, SU:2 with buccal mucosa graft is often chosen. Since grafts represent the replacement of non-vascularised tissue, they are dependent upon a healthy recipient bed for survival. There are some reports of possible risk factors that may affect the outcome of urethroplasty, although the findings are far from consistent (55, 56). It would be interesting to analyse the risk factors for urethroplasty techniques specifically used for the penile strictures, which often are long and complex.

### Penile skin flaps (SU:1)

Penile skin flaps according to the Orandi technique can be applied to strictures that lie within the region from the meatus to the bulbar urethra (57), although the outcomes vary (Figure 14.). However, it is of importance that the flap is hairless otherwise this condition may lead to stone formation, chronic bacterial colonisation and increased inflammation. To harvest the flap, it is necessary to hold the penis stretched and remember to handle the tissue carefully using fine instruments and a bipolar electrocautery, as haematoma formation can compress the vascularity of the pedicle. The length and width of the urethral defect is measured after the stricturotomy.

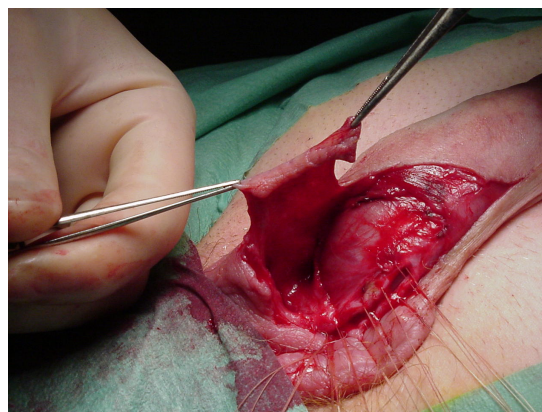


Figure 14. Penile skin flap.

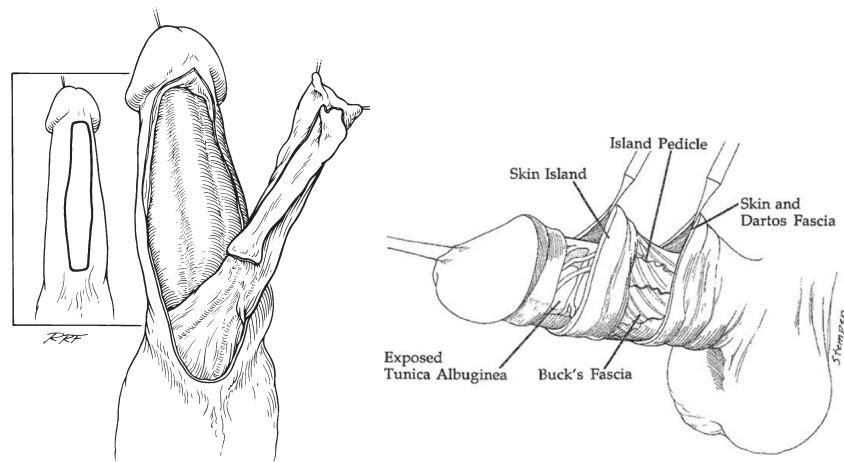


Figure 15. These images illustrate the longitudinal (Orandi technique) and circular flap (McAninch technique) techniques with dartos fascia mobilisation. (Urethral reconstruction; Chapter 18; by KJ Carney and JW McAninch)

A ventral flap can be oriented either transversely or longitudinally. Circular skin islands from the prepuce, if the patient is not circumcised, may sometimes be used, and they allow up to 15 cm of pediculated flap. (Figure 15 and 16.) However, it is not yet clearly defined if one approach is superior over another in reconstructive urethral surgery. The flaps from the penile or scrotal skin might have been harvested randomly, and this is because there are no defined arteries. To create an extensive dartos pedicle, the harvesting become time-consuming and produces scarring, and abnormal contouring of the penis may appear.

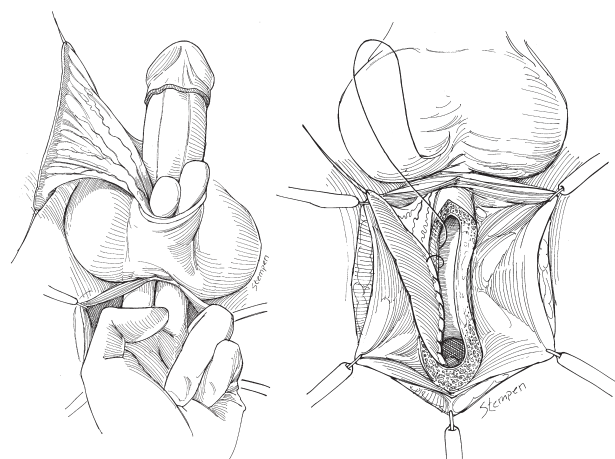


Figure 16. Mobilisation and suturing of the pediculated flap. (58)

Before the 1990's, some surgeons still believed that a flap was more reliable because of the blood supply of it's own, but today free grafts have regained their place with knowledge, inter

alia the study of Burger's (11). There is no real difference between the use of flaps and grafts in terms of restricting (59). In the absence of any contra-indication, it is easier and faster to use a graft, why this procedure is of choice by the majority of urethroplasty surgeons.

### Free graft (SU:1)

The buccal mucosa (BM) is preferred as a substitute tissue, having gained popularity in the 90's (60). Before this, the penile skin was the recommended substitute material for penile and bulbar urethroplasties. BM is similar to the epithelium of the penile urethra, in that it has three layers, starting with a thick and avascular epithelium that contains keratinocytes, followed by the lamina propria with vascular connective tissue that contains fibroblasts and submucosal connective tissue that is attached to the linked muscles, glands and fat structures. The BM is highly resistant when exposed to stretching, compression and shearing forces.

Some of the advantages of BM are that it is easy to harvest without visible cosmetic deficit and the thick epithelium is accustomed to exposure to saline solutions. Most patients do not experience pain in the mouth and would undergo the procedure again (61, 62), even though a minority of patients experience oral numbness and tightness in the mouth, issues that the patient must be informed about before surgery. An incision over the scar in the mouth to relieve the tightness may be necessary in some patients. Before harvesting the BM, the mouth of the patient is examined carefully to evaluate the oral mucosa of the cheek, the capacity to open the mouth, and the presence of any mouth diseases (e.g. candidiasis or herpes virus infection). In patients who chew tobacco or pan masala, submucosal fibrosis may appear in the cheek, in these cases harvesting from the tongue is required. Chlorhexidine mouthwash procedure for oral cleaning some days before surgery is a custom for patients in some clinics. There are three possibilities to harvest BM in the mouth: from the cheek; from the tongue; and from the lip. Collecting the BM from the lip can have negative aesthetic consequences, therefore not performed as much because of unsatisfied patients.

Nasal intubation is preferred when harvesting the oral mucosa. However, it is possible to harvest the BM when normal intubation is present. The use of a mouth retractor might be useful, with some surgeons using only a rubber wedge between the teeth or sutures to hold the lips apart and to stretch the oral mucosa. Stensen's duct is located at the level of the second upper molar, often marked using a pen before harvesting. Graft size, which is a standard of approximately 4 cm in length and 2,5 cm in width, is also marked on the oral mucosa in an ovoid shape and depends on the length of the urethral incision. NaCl 9% or lidocaine 1% with adrenaline is injected just under the buccal mucosa, to enhance haemostasis and to lift the graft from the muscle bed thereby facilitating the harvesting. When the graft is dissected and removed, closure is often performed with a vicryl rapid 4-0 suture, although some leave the incision open. The graft is trimmed from muscle and fat tissue, sometimes even fenestrated and adjusted according to site, size and length. The same procedure is used for harvesting BM from the tongue, although care must be taken not to damage the Wharton's duct or the lingual nerve.

Grafting is executed in two phases, where the first phase involve imbibition, when the graft absorbs nutrients from the plasma at the surface of the graft bed. The second phase entails inosculation of the microvasculature that is important for ensuring that the graft takes and is not sloughed off.

Regarding the bulbar strictures, the grafts can be positioned ventrally, laterally or dorsally. In this cohort the majority of the bulbar strictures had a ventral approach primarily and a dorsal approach secondarily. The surgery started with dissecting of the bulbar urethra from the corpora cavernosa, after which the dorsal or ventral surface was opened. Stricture length is

evaluated and measured. Careful examination is needed to assess the stricture site, glans, penile skin and prepuce. If the stricture is distally including the meatus it is necessary to open along the penile skin from the meatus on the ventral side proximally to the healthy urethral tissue. Thereafter, a midline incision on the dorsal side of the urethral plate is made longitudinally down to the albuginea of the corpora so as to create a wide bed for the graft, which is quilted into the bed, then tubularized over a silicone catheter Ch 16, what is called the Asopa technique (63). (Figure 17.)

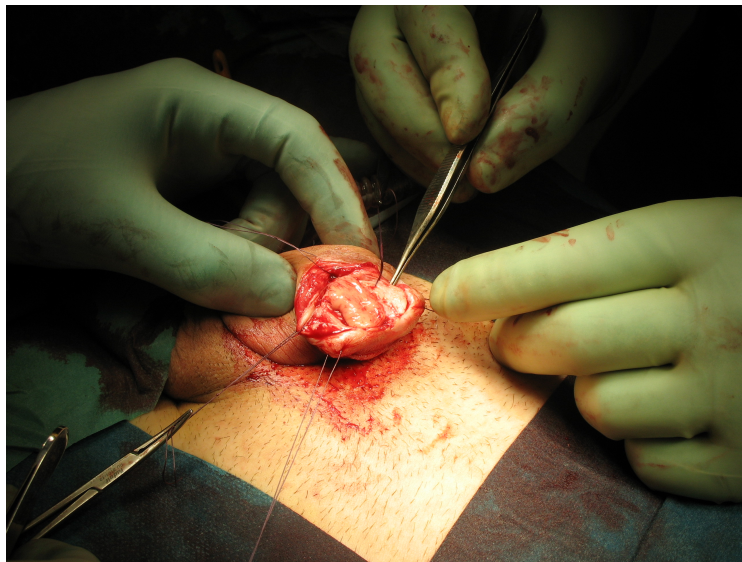


Figure 17. A buccal mucosal inlay graft in a distal penile stricture performed according to the Asopa technique.

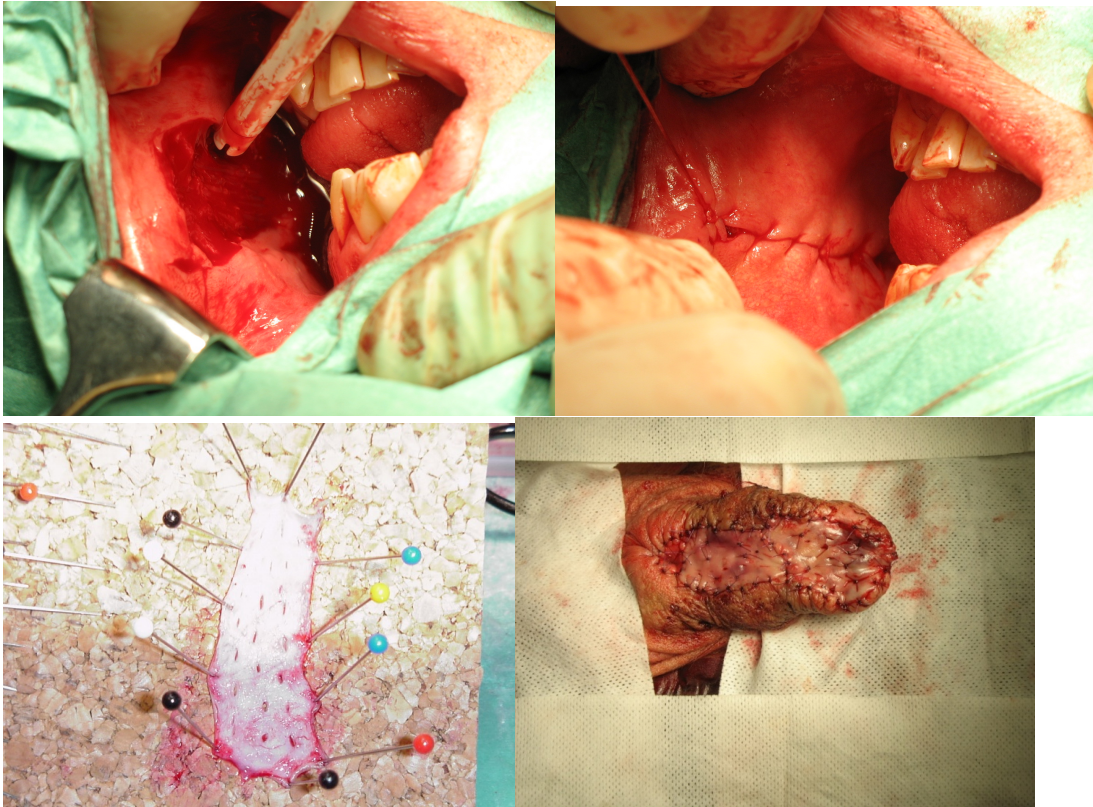
If the stricture does not affect the meatus two techniques can be used. The first technique is to make a circumcision incision and degloving of the skin of the penis that opens up for dissection of the urethra. When the stricture is identified, the urethra is opened by a midline incision ventrally until healthy tissue appears and followed by the same procedure as above. The second technique, starting with a perineal incision and invaginate the penis into the perineum to start the dissection of the urethra. With this procedure the urethra is usually dissected on one side from the corpora cavernosa and opened dorsally, after which the graft is adapted to the urethra and quilted to one of the corpora cavernosa. Thereafter, the penis is after that reinvaginated and a urethral catheter is inserted.

### **Two-stage substitution urethroplasty (SU:2)**

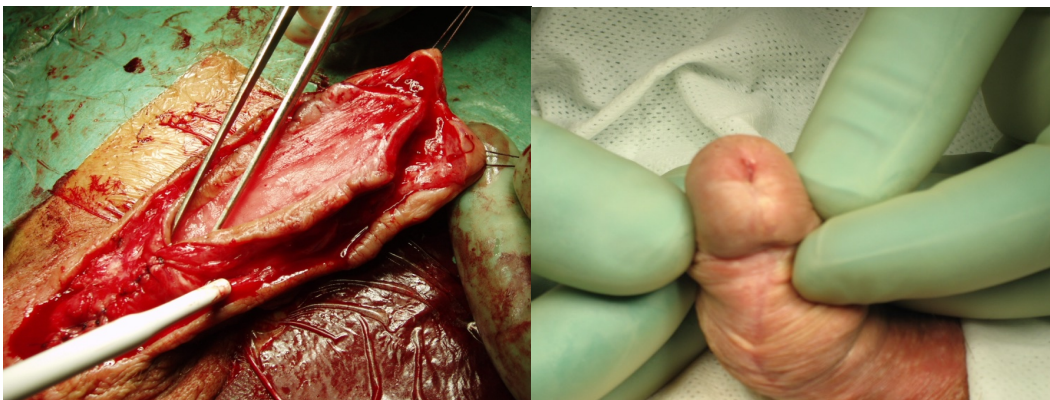
Patients with complex and long penile strictures (especially panurethral strictures) with failed hypospadias surgery or LS that involves the skin of the penis having scar formation and where the Dartos fascia is absent or massive fibrosis is present, one-stage repair would yield a poor success rate. This is why two-stage procedure is necessary in these cases. (Figure 18.)

The stricture, as well as the abnormal urethra with scar tissue, is completely excised and a temporary urethrostomy is created. After measurement of the stricture length, a decision is made to use one or two buccal mucosal grafts. The underlying fatty tissue is removed from the graft, which thereafter is meshed. After graft suturing, a firm dressing is applied for 5 days to prevent the development of underlying haematomas. After 4–6 months the second stage procedure is performed with tubularisation of the graft, followed by placement of a 16 Ch

catheter for 12 days. If the urethral plate is not approved, stage one is repeated. Some elderly patients and those who have received multiple urethroplasties may be content with just the first stage and may not wish to undergo the second stage.



STAGE 1.



STAGE 2.

Figure 18. Two-stage urethroplasty with buccal mucosa for a panurethral stricture. Stage 1; graft harvesting and patching the graft. Stage 2; tubularisation and the results obtained after one year.

### Excision with end-to-end anastomosis (EA)

Usually, EA is performed exclusively for bulbar strictures. Short strictures, of less than 2 cm, are ideally suited for an excision together with a spatulated end-to-end anastomosis. Both

bulbar and membranous stricture can develop after a trauma, such as a straddle injury in the former case, and a pelvic fracture in the latter case. In the literature sexual dysfunction has been reported after transection of the urethral bulb, although the findings are far from uniform (64-71). The question has been put forward as to whether SU should be preferred over EA in order to minimise the risk of sexual dysfunction.

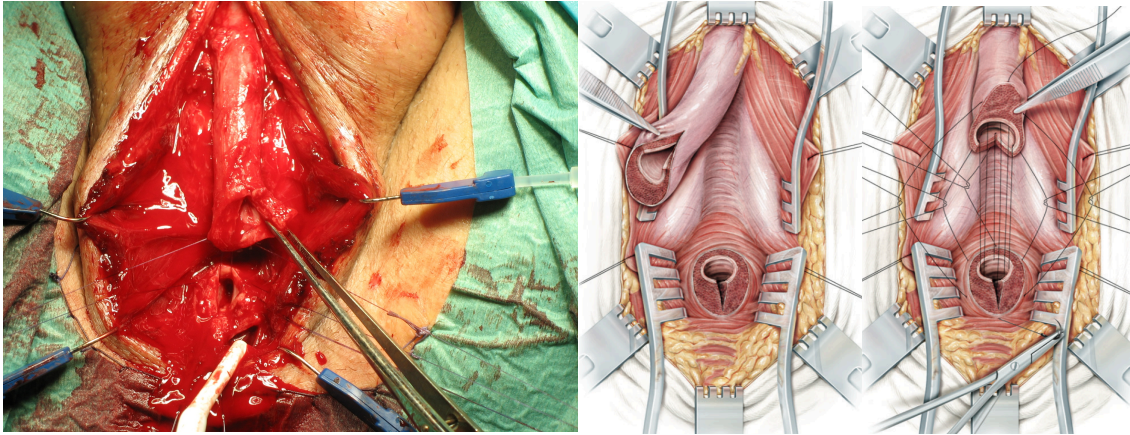


Figure 19. Bulbar urethra is transected/excised and spatulated, then sutured. (Surgical atlas anastomotic urethroplasty, Anthony R. Mundy, BJU International, 2005, 96;921–944.)

Careful dissection is performed, mainly dorsal of the bulbar urethra. After mobilisation, the bulbar urethra is cut at the stricture level. The incision in the tunica albuginea is made a few millimetres distal, to create a firm edge for second layer closure. After the fibrotic part of the strictured urethra is resected, the ends are spatulated, one ventrally and the other dorsally. (Figure 19.) A study that compared different combinations of spatulation found that distal-dorsal and proximal-ventral incision had success rate of 96% and 88%, respectively (72). However, this finding was for pelvic fracture patients and was not validated for non-traumatic bulbar strictures. The anastomosis is created with 6 to 8 interrupted 4-0 polyglyconate sutures. The first 3 sutures, located at the 10, 12 and 2 o'clock positions, respectively, are placed from inside and the others were placed from outside. (Figure 19.) When the first 3 sutures are made, a 16 Ch silicone urethral catheter is introduced. After the mucosal anastomosis is finished, an outer running suture of tunica albuginea is made. This created a second layer with the suture line a few mm distal because of the incision described. Some use drainage and other use a cross-formed compression bandage in the perineal region for two days to inhibit a hematoma. In our cohort we used cross-bandage. The patients are advised not to practise sexual activity for six weeks in most departments. Antibiotic and thrombolytic drugs used postoperatively see Paper I-II.

In traumatic bulbar and membranous strictures with massive fibrosis and longer than two cm the stricture tissue is excised and it might be hard to do the anastomosis without tension. However, there are ways to shorten the path for the urethra, to make it tension free, with an inferior wedge pubectomy (Figure 20.) or re-route the urethra (Figure 21.) around the crus at the peno-bulbar junction to straighten the natural curve and a combined EA with graft augmentation (68) (Figure 23.).



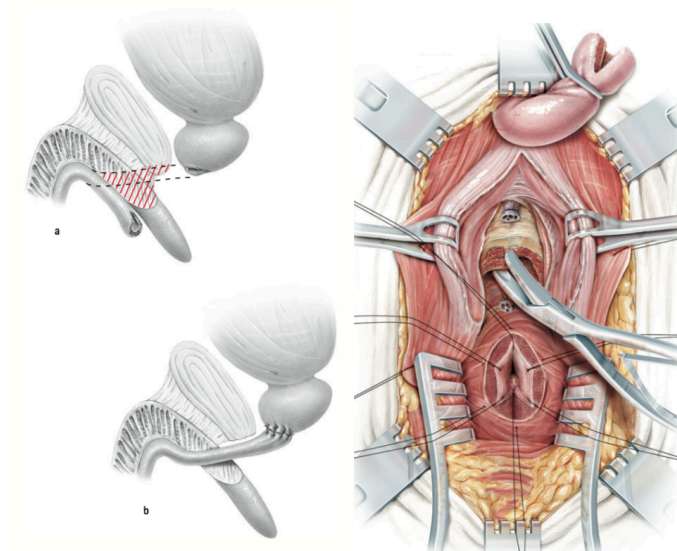


Figure 20. Incision down to the pubic symphysis and excision of a wedge of the bone with a double action bone nibblers. (Surgical atlas anastomotic urethroplasty, Anthony R. Mundy, BJU International, 2005, 96; 921-944.)

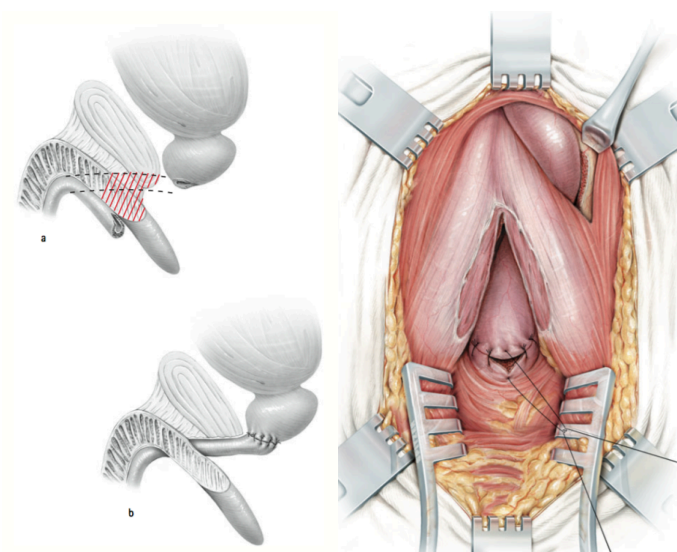


Figure 21. The crus of the penis can be detached from the pubic periosteum, to expose the inferior pubic ramus and gouge out some bone and a tunnel around the crus of the penis allow a tension free anastomosis. (Surgical atlas anastomotic urethroplasty, Anthony R. Mundy, BJU International, 2005, 96; 921-944.)

The question of whether to transect the bulbar urethra or not in non-traumatic bulbar strictures has been raised. This may affect blood and nerve supply to the penis so erectile dysfunction might develop, which have encourage surgeons to evolve other surgical techniques, such as resection without transection (73, 74) (Figure 22.)

The surgical technique for non transecting bulbar urethroplasty, starts with the same perineal incision and the bulbar urethra is dissected off the tunica albuginea of the corpora dorsally by dividing Buck's fascia on either side and mobilizing it from the distal margin of the bulbospongiosus muscle to the perineal membrane.

To prevent the main bulbar arteries there is no need to mobilise the bulb of the corpus spongiosum from its attachment to the perineal body. An incision is made longitudinally over the stricture in the dorsal midline extended into healthy normal calibre urethra both distally and proximally. Then the stricture is excised and closed on the inside with interrupted 5-0 polyglycolic acid suture with the knots on the inside. The dorsal longitudinal stricturotomy is closed transversely with knots on the outside as a 'Heinke-Mikulicz' type strictureplasty, used in gastro-intestinal surgery (75) (Figure 22-C).

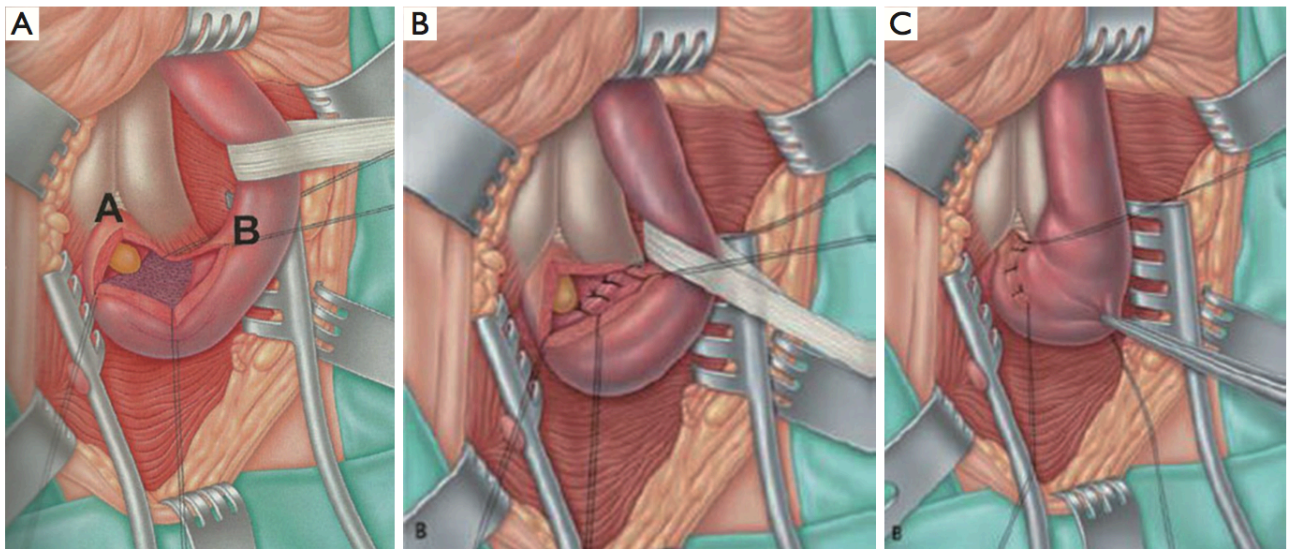


Figure 22. The stricture is excised (A) and the urethra sutured on the inside (B). A horizontal closure of the stricturotomy incision (C). (Non-transecting anastomotic bulbar urethroplasty: a preliminary report, Daniela E. Andrich, Anthony R.Mundy, BJUI, 2011.)

### EA and SU combined

When using the augmentation technique both EA with SU are performed (Figure 23.). Then the dorsal spatulation are sutured around a full thickness graft of buccal mucosa or skin graft quilted onto the tunica albuginea. Closing the ventral hemi-circumference with full thickness interrupted sutures, which brings the ends of the urethra together, performs completion of the anastomosis.

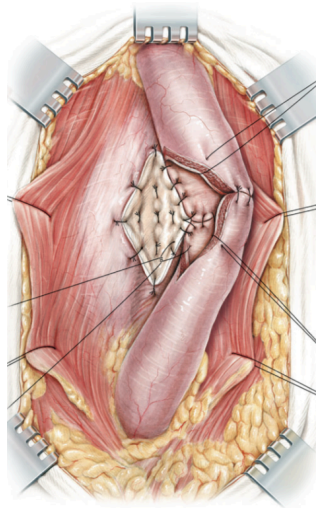


Figure 23. Augmentation technique with a graft of bulbar urethral stricture. (Surgical atlas anastomotic urethroplasty, Anthony R. Mundy, BJU International, 2005, 96;921-944.)

### Perineal urethrostomy (PU)

PU is a stoma of the urethra under the scrotum. The procedure starts with an upside down U-shaped perineal incision and the bulbar urethra is exposed and ventral urethrotomy and closure of the distal spongiosum tissue. The proximal urethral opening is calibrated. The perineal u-flap is adapted and sutured to the proximal urethral mucosal edge. The perineal skin margins are also sutured to the bulbar urethral plate margins. After this a catheter is left in place for 10 days (Figure 24.).

PU might be the final solution when all other types of surgeries for urethral stricture have failed or deemed unsuitable by the surgeon or the patient. Some patients with a temporary PU are satisfied after one stage surgery and do not always show up for the tubularization part, second stage. Patients with bad health, co morbidities and not suitable for repeated surgery, should probably be offered a perineal urethrostomy earlier.

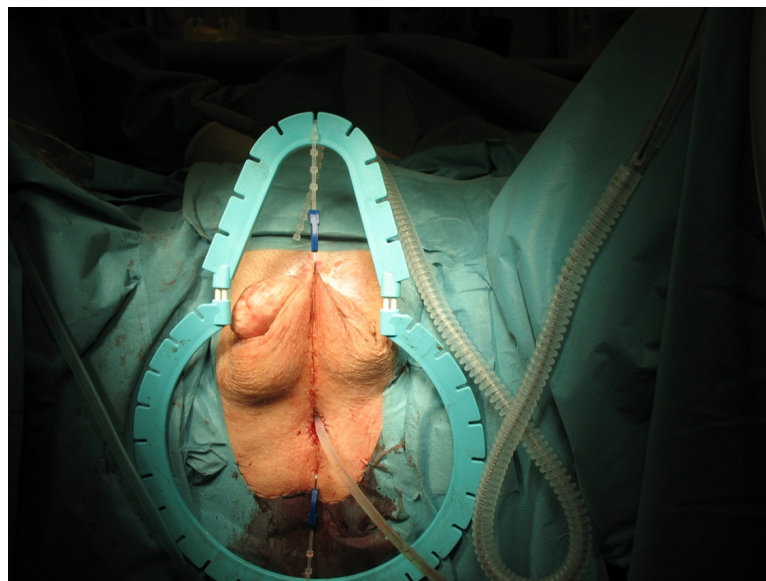


Figure 24. Perineal urethrostomy.

## COMPLICATIONS

### Restrictures

The reviews of the literature in urethroplasty cohorts tell us that the risk for stricture depends on multiple factors, such as the location and length of the stricture, previous urethral surgery and the technique used. Even smoking and diabetes may influence the success rate (56). Restrictures after onlay urethroplasty appear as short white rings often both distal and proximal of the graft margins (76), also happening in anastomotic restrictures usually short stenotic rings, which might be treated with one DVIU, eventually they're lacking evidence for this matter. Longer restrictures needs a new urethroplasty or a perineal urethrostomy (77). "Urethral rest" has been suggested before urethroplasty treatment, since self-catheterization and dilatation of urethral strictures may aggravate the injury and cause excessive inflammation and fibrotic formation in turn causing underestimation of the stricture length. Therefore it might be beneficial to avoid these procedures and instead use suprapubic drainage for approximately three months prior to urethroplasty surgery to improve the results (78).

### Erectile dysfunction

The surgical procedures, such as dissection into the crural space and extensive mobilization of the corpus spongiosum, may affect the patient's sexual function (67, 70, 79) resulting in erectile dysfunction (ED). Other factors influencing on the erectile function are the patient's age, diabetes (giving numbness distally in limbs, such as the glans), again stricture length and location, also the type of urethroplasty and the time that have passed since the surgery. The difference between penile and bulbar urethroplasty is that, penile side effects is more aesthetic with penile chordee and tethering, whilst the bulbar side effects comprise the risk of harming the neurovascular structures. One study suggested that long penile strictures treated with skin flap resulted in a high ED rate (80). Erickson et al noted a high rate of postoperative ED, but the majority (98%) regained normal erectile function after a mean of 190 days (66). A similar study showed a 10 % ED after SU that decreased to 2 % after 3 months (81). Barbagli et al reported in a retrospective study in 2007 about 153 cases of EA urethroplasty with 23 % ejaculatory dysfunction, 20 % decreased glans sensitivity and 12% ED (69). Other studies show low incidence of ED, 1-2.3% (82, 83). In augmented EA series there have been reported up to 17 % of penile shortening (84), even though a small cohort of 29 patients. This has made some authors to use muscle-sparing and nontransecting techniques for urethroplasty. In contrary, buccal mucosal grafts for urethroplasty show a minimal risk for ED (85, 86). However, ejaculatory problems may occur when the semen may be retained in the graft segment, especially in ventral position (87). The urethral sacculation that may occur, when fasciocutaneous flaps are used for urethroplasty, also increase the incidence of dribbling. However, less common when placed dorsally. The patient may use self-compression of the perineum after voiding to improve micturition.

### Penile shortening and angulation

Penile shortening and angulation can appear after excision of bulbar strictures, particularly if resection encompasses too much of the urethral tissue without supplementing the procedure with an augmentation. The erection may be more forward than upright. This has, in the vast majority of cases, no functional significance, however the patient may be in need of reassurance. Infrequently patients, with significant curvature and angulation, may be offered redo surgery in order to correct the disfigurement.

## Infection

Urosepsis and urinary tract infection can be expected after urethroplasty surgery, as after any surgery. Catheters should be removed as early as possible and appropriate antibiotic prophylaxis should be used. Stone and hair may be in the sacculation after substitution urethroplasty in the urethra, causing infective symptoms as dribbling and recurrent urinary infections, which require revision of their urethroplasty.

## Haematoma

There is a minor risk for hematoma at the incision site postoperatively. Some surgeons put drainage into the perineum while others put on a compression dressing. If a hematoma occurs this may develop into an infection forming an abscess that need to be incised and treated with antibiotics.

## Penile skin necrosis

This complication usually occurs in the penile skin proximal to the flap, due to the disturbed vascular supply of the skin when harvesting the flap. Up to 15 % may have penile skin necrosis after fasciocutaneous skin flap urethroplasty (88), usually because of disturbed vascular skin supply. Usually it heals and it is of importance to reassure the patient that the condition will normally resolve without any sequel, despite the temporarily necrotic presence of the penis.

## Fistula formation

It is a rare condition after bulbar urethroplasty because of the thick subcutaneous layers in the perineum. It is more common after penile reconstructions, due to thin tissue layers or even lack of layers between the urethra and the penile skin. When using a flap as a graft 20 % of the patients (81, 86) end up with fistula formation, and after free grafts with buccal mucosa it is 10 % (89). Fistula formation may appear due to postoperative erection, which may open the sutures, which is difficult to avoid. There are some suggestions on about how to prevent this, the report of fewer fistulas in urethroplasties when using monofilament sutures (PDS) in one study (90), however this was refuted by others (91). To overcome fistula formation, one must avoid overlapping sutures as much as possible and cover the suture with several layers of Dartos or with a tunica vaginalis flap (92). Wound infection, resulting in necrosis of the skin and the graft, can also form fistulas; it is less common in dorsal compared to ventral skin flap urethroplasties (93). Small fistulas can be resolved spontaneously needing an extended time of catheterisation and proper wound care.

## Buccal mucosal graft-related complications

This may be used for long bulbar strictures as well as long complex penile strictures, almost replacing the skin grafts and decreased the use of fasciocutaneous skin flaps.

Extensive harvested grafts increase the risk of donor site morbidity, such as damage the salivary duct or nerves. There can be early complications such as pain, numbness, bleeding which develops as a swollen cheek, which in turn might form scars with contraction leading to a tight jaw opening with following speaking disorders in the worst cases. Studies performed on late complications include persistent oral tightness (9-32%) in 6-20 months

after surgery or oral numbness (2-26%), change in salivation (1-11%) or rare complications such as Stensen's duct damage (94, 95). It is of high importance to mark the duct of the salivary gland before injecting the saline solution for lifting the buccal mucosa up from the muscle layer. If insufficient BM one might consider using penile lip or lingual mucosa, which has higher complications than cheek harvesting (96-98), however, tongue numbness, taste disturbances and slurred speech may occur (99).

There is no consensus about injecting the buccal site with adrenaline or not, however, some studies showed a decrease postoperatively symptoms when leaving the cheek wound open allowing it to heal secondary, which changed the practice to leave the wound open in some of the reporting centres (100-102).

Some harvest the graft before placing the patient in the high leg position, when it is obvious that a buccal graft is needed, in order to minimize the risk for compartment syndrome and other position related complications.

### **Positioning complication**

High legs position, also called lithotomy position, can cause nerve injury 1.5-16%, as well as compartment syndrome (CS), where the duration of surgery was the only significant factor (103-105). External decompression devices reduce the risk for CS; risk factors for development of CS being intraoperative hypotension, blood loss, peripheral vascular disease, prolonged operation > 4 hours, muscular calves and high BMI (106, 107). After each operation palpation of the calves is necessary for early diagnosis of CS. This is of great importance, as a rapid fasciotomy will help avoid permanent limb disability.

## **AIMS OF THE THESIS**

During the last decades there have been a number of improvements of urethroplasty techniques. Over the next years these trends are likely to linger. Some patients have more or less full-length stricture with a variance of obliterations, in addition often have had repeated urethroplasties. There is no guideline for these patients and alternative approaches must be considered.

The overall aim of this thesis was to explore the differences between the techniques of urethroplasty, the risk factors for failure, the risk for sexual dysfunction and the pathophysiology. Hopefully this will help us to evolve alternative approaches that in turn will lead to a better care of our patients. The specific aims of each paper were as follows:

### **Paper I**

To analyse the risk of sexual dysfunction after transecting the bulbar urethra and the outcome of excision with anastomosis and substitution urethroplasty.

### **Paper II**

To disclose possible risk factors for failure in penile stricture surgery and to analyse the outcome of substitution urethroplasty.

### **Paper III**

To evaluate the fate of failed primary urethroplasties and the need and types of re-intervention.

### **Paper IV**

To describe the pathophysiology and to categorise the fibrosis of bulbar stricture and to disclose whether or not the degree of fibrosis is a predictive factor for the outcome after open bulbar urethroplasty.

## PATIENTS AND METHODS

### General considerations

The cohort was based on chart reviews of all identified men with urethral strictures, who had undergone urethroplasty surgery between 1999-2013, totally 569 procedures. Year 2014 was also included in Paper IV. This was managed with registered operation codes at the Sahlgrenska University hospital. The characteristics of the populations in paper I-IV is presented in Table 1. The follow-up regimens were the same in paper I-IV with 3, 12 and 24 months, and only at patient request thereafter. After 24 months, if satisfied, the patient were discharged from the follow-up program and instructed to contact the clinic if micturition problems should occur. In our clinic at Sahlgrenska this way of follow up works very well, therefore if the patient experience problems with the micturition, he will contact us directly or habitually be referred back from the district doctor to our clinic. So for example if a patient was operated in 2010 with success and discharged in 2012 without any urinary problems and the patient did not contact the clinic in any way. To analyse the follow up time in this scenario, we calculated from the operation date 2010 to endpoint date of the study 2016, because of the natural event that if there were a problem for the patient he would have had contacted us. Therefore, he is still a success in 2016, even if he has not been followed up since 2012. This way of follow up is possible because of two things. First, when you cannot micturate you will go to the ER of a hospital. Second, Sweden is a small country with good medical coverage and a few centres perform open urethroplasties, so the patient will be referred back to our clinic. There may be some patients, who have moved out the country off course, that we miss to follow up but they are scant.

The stricture recurrence was diagnosed at cystoscopy examination during follow up, urinary flow and the patient's symptoms with poor stream, dribbling or as bad as urinary retention. Sometimes an 8 Ch semirigid ureteroscope was needed when severe obliteration occurred, but even this was impossible in some occasions and in these cases combined retro- and antegrade urethrography was performed. Failure was defined as the need for a new surgical intervention such as dilation, DVIU or a new open urethroplasty. Two surgeons, Lars Grenabo and Klas Lindqvist, performed all urethroplasties. The statistical tests were two sided and p values < 0.05 were considered significant. The protocol of all the studies was approved by the University of Gothenburg regional ethical review board (663-11). The statistical calculations were consistently performed with SPSS for Mac.



	Paper I		Paper II		Paper III		Paper IV		
	EA	SU:1	SU:1	SU:2	Bulbar	Penile	FG I	FG II	FG III
<b>No op</b>	94	75	80	29	56	26	19	13	13
<b>Age, mean /median, years</b>	Mean 44 (16–75)	Mean 42 (19–74)	Mean 50 (19–79)	Mean 54 (20–77)	Median 41 (16–80)	Median 50 (20–78)			
<b>Follow up, mean/median, months</b>	Mean 41 (12–87)	Mean 69 (12–132)	Mean 63 (13–144)	Mean 40 (15–118)	Median 65 (6–188)	Median 77 (15–181)	Median 19 (9–54)	Median 18 (7–26)	Median 37 (15–50)
<b>SL, mean, cm</b>	1.5	1.5	3.5	4.5	2	4	-	-	-
<b>Type of surgery</b>									
<b>IU</b>					X	X			
<b>Dilation</b>					X	X			
<b>EA</b>	X				X	X	X	X	X
<b>SU:1</b>		X	X		X	X			
<b>SU:2</b>				X	-	X			
<b>PU</b>					X	X			
<b>Total Patients</b>	161		90		82		45		
<b>Time period</b>	1999-2009		2000-2011		1999-2013		2011-2014		
<b>Type of stricture</b>	Bulbar		Penile		Bulbar /penile		Bulbar		
<b>Type of cohort</b>	Retrospective		Retrospective		Retrospective		Prospective		

Table 1. The characteristics of the populations in paper I-IV.

EA excision and anastomosis; SU:1 substitution urethroplasty; SU:2 two stage substitution urethroplasty; FG fibrosis grade; SL stricture length; DVIU direct vision internal urethrotomy; PU perineal urethrostomy.

## Paper I

We retrospectively reviewed the charts of all 169 bulbar urethroplasties performed in 161 patients at our institution in the period from 1999 to 2009. A total of 94 resections followed by anastomotic repair and 75 substitution urethroplasties with onlay technique, mostly ventral, with free grafts using skin (N=64) or BM (N=11). Of the onlays, 58 were performed before 2005, and the 91 transections were performed after 2005. In the transection and onlay groups, the mean ages of the patients were 44 years (16–75) and 42 years (19–74), respectively. The mean follow-up periods were 41 months (12–87) and 69 months (12–132), respectively. The mean stricture length in both groups was 1.5 cm. All except seven patients previously underwent one or several internal urethrotomies, and 13 patients were previously treated with urethroplasty. Complications other than sexual dysfunction were not highlighted in this report. Patients were followed up as described in the *General considerations* section above. The physician questioned each patient verbally about sexual function at each visit during the follow-up period; the responses obtained after at least one year of follow-up are presented. The questions, which were dichotomous (yes/no), covered the topics of erectile dysfunction, penile shortening/angulation, glans filling, glans sensibility and ejaculatory function. No validated questionnaires were used. Failure was defined as the need for new surgical intervention, such as dilatation, internal urethrotomy or a new open urethroplasty. Stricture recurrence was diagnosed by cystoscopy during the follow-up, in combination with assessment of patient symptoms, such as a poor urine stream, dribbling, low urinary flow and urinary retention. Pre-operatively all of the patients underwent urethroscopy, with an 8 Ch semi-rigid ureteroscope being employed when needed. For those patients in whom this could not be done, combined retrograde and antegrade urethrography was performed. Urinary tract infections were eradicated before surgery. Pre-operative antibiotics i.e., trimethoprim sulpha or a quinolone, were administered and continued during the catheterisation period, and 3 days after de-catheterisation. An anticoagulant was also administered as a standard treatment and throughout the hospital stay, normally 2 days postoperatively. The surgical techniques used in the study are described under Patients and Methods in Paper I. No drainage was used. Instead,

a cross-formed compression dressing was applied to the perineal region for 2 days (Figure 25.). Free mobilisation was recommended for all the patients. The catheter was routinely removed after 14 days without urethrography follow-up. Patients were advised to abstain from sexual activity for 6 weeks post-operatively.

*Statistical analyses:* The Kaplan-Meier method for survival and the log-rank test were used for time to failure. Statistical significance was adjudged for differences with  $p$  values  $<0.05$ .



Figure 25. Cross-formed compression applies to the perineal region after urethroplasty surgery.

## Paper II

We retrospectively reviewed the charts of all urethroplasties conducted during the period 2000-2011 at Sahlgrenska University Hospital for correction of penile urethral stricture, which was defined as a stricture located distal to the separation of the crura. In total, 109 procedures in 90 patients were included in the study. Isolated meatal strictures were not included, as conventional urethroplasties are not performed on these patients. Overall, 80/109 procedures involved a one-stage procedure with a skin graft, the Orandi technique (N = 68) with a skin flap, a free graft of buccal mucosa (N = 9) or a free skin graft (N = 3). Twenty-nine two-stage procedures (SU:2) were performed in patients with more complicated strictures. In this group, 12 patients had LS. The second stage in SU:2 was designated as the operation date when calculating the follow-up time. The following possible risk factors were analysed: stricture length; age; body mass index (BMI); LS; hypospadias; previous internal urethrotomy/previous urethroplasty; and clinical experience. The reason why the hypospadias group was separated from those who had undergone previous urethral surgery was the anatomical difference in these patients, due to defective closure of the penile shaft. Six patients died during the study period and all of the patients had a follow-up period of more than 12 months.

Patients were followed-up as described in the *General considerations* section above. Failure was defined as the appearance of a new stricture or a fistula that required a surgical intervention, such as dilatation, DVIU or a redo urethroplasty. Stricture recurrence or fistula appearance was diagnosed by cystoscopy during the follow-up, in combination with

examinations of the patient's symptoms, e.g., poor urine stream, dribbling, leakage, low urinary flow or a urinary retention episode. An antibiotic was given immediately preoperatively. An anticoagulant was administered as standard practice throughout the hospital stay. There were no obvious indications for choosing one surgical procedure over the other. The indications varied throughout the study period for the different procedures, depending on the experience, gained by the authors and others. For example, using a two-stage procedure in patients with lichen sclerosus was used more frequently in the late phase of the study period. One-stage urethroplasty was mainly carried out using the technique described by Orandi, with a pediculated penile skin flap. Furthermore, nine free buccal grafts and three free skin grafts were used. The free grafts were positioned dorsally or laterally on one of the cavernosal bodies. Five free grafts were sutured perineally after inverting the penis behind the scrotum, in the late phase of the study period from 2011 and onwards. All the suturing was performed using 4.0 or 5.0 running polyglyconate sutures. A 16 Ch silicone urethral catheter was introduced when one side was sutured, and was left in place for twelve days. During two-stage urethroplasty the stricture, and the abnormal urethra with scar tissue, were completely excised and a temporary urethrostomy was created. After measurement of the length of the stricture, a decision was made to use one or two BM grafts. The grafts were cleaned of underlying fatty tissue and meshed. After graft suturing, a firm dressing was applied for 5 days to prevent the development of underlying haematomas. After 4–6 months the second-stage procedure was performed with tubularisation of the graft, followed by placement of a 16 Ch catheter for 12 days. Free mobilisation was recommended for all the patients. Antibiotics were administered from the day of surgery until three days after removal of the catheter. Urethrography before catheter removal was not performed routinely, but limited to selected cases. Patients were advised to abstain from sexual activity for six weeks postoperatively.

*Statistical analysis:* The possible associations with surgical outcome were examined using univariate and multivariate binary logistic regressions. Proportions in categories were compared using Fisher's exact test. All statistical tests were two-sided and  $p$ -values  $<0.05$  were considered statistically significant.

### Paper III

A retrospective chart review was carried out that comprised all urethroplasties performed for correcting urethral strictures during the period 1999–2013 at Sahlgrenska University Hospital. Primary reconstructions of meatal strictures were not included. During this period, 407 patients were identified. Of these, 82 patients had failures, defined as requiring reintervention. The patients' characteristics are listed in Table 1 in Paper III. Of the failures, 56/290 (19%) were originally treated for bulbar stricture, and 26/117 (29%) for penile stricture. Of the 26 penile stricture failures, 7 had no stricture but did have a urethrocutaneous fistula. Redo procedures performed during the period 1999–2015 included endourological procedures, such as dilatation and DVIU.

The redo urethroplasties comprised: excision with anastomosis; substitution urethroplasty using fasciocutaneous skin grafts or free patches with skin or BM, two-stage procedure with BM and as a final procedure, perineal urethrostomy. Follow-up was carried out as described in *General considerations* section above. The chart reviews were collected from the referral hospitals when necessary. Failures were defined as requiring reintervention, such as dilatation, DVIU or a new urethroplasty. Patients who had a PU or permanent clean intermittent self-dilatation (CISD) and those placed on a waiting list for a new redo surgery,

and who had not been handled during follow-up at the end-point date of the study, were considered as end-point failures. Complications were not highlighted in this paper.

*Statistical analysis:* Not applicable, solely descriptive analyses.

#### **Paper IV**

This prospective study included 45 men with a bulbar urethral stricture who were subjected to EA urethroplasty, as described above under surgical procedures, between 2011 and 2014 at Sahlgrenska University Hospital. The removed urethral tissues were analysed directly by a urologist after the specimens were fixated in 10% neutral- buffered formalin, dehydrated and embedded in paraffin. The sections were measured in 4 µm and stained with Haematoxylin-Eosin, van Gieson and Masson's trichrome. The diagnosis was re-evaluated by the same urologist at least 2 years after the last patient was included in the study. The pathologist was blinded to the original diagnosis and as well as the study design. Fibrosis was classified into grade I-III (mild, moderate and severe, respectively). Comparisons were made with two resection specimens of normal urethra from patients who had undergone sex-change surgery, i.e., penectomy. The definitions of normal urethra, fibrosis and sclerosis can be found in the *Materials and Methods* section in Paper IV.

*Statistical analysis:* Fisher's exact test was used for the statistical comparisons, due to the size of the study, which were done with the SPSS, ver. 23 for Mac software. All statistical tests were two-sided and  $p$ -values  $<0.05$  were considered statistically significant.

## RESULTS

### Paper I

One patient in each group developed erectile dysfunction (ED) postoperatively as illustrated in Table 1. The patient with ED in the EA group had a BMI of 48 (kg/m<sup>2</sup>), and the patient in the SU group was 74 years old. Five patients developed penile angulation/shortening in the transection group, were four of the five patients whom had strictures that were localized to the distal half of the bulbar urethra, although they did not report interference with sexual function. For more details of the characteristics of the patients with ED and angulation, see Table 2. No patient complained of impaired glans filling or sensibility, or ejaculatory dysfunction. Figure 26 illustrates the recurrence-free rate after transection with anastomosis and onlay urethroplasty after 12–134 months, as well as the success rates for both groups. The success rates for the EA group and the SU group were 91% and 71 %, respectively. The mean times to a redo procedure due to failure were 10 and 17 months in the EA and SU groups, respectively.

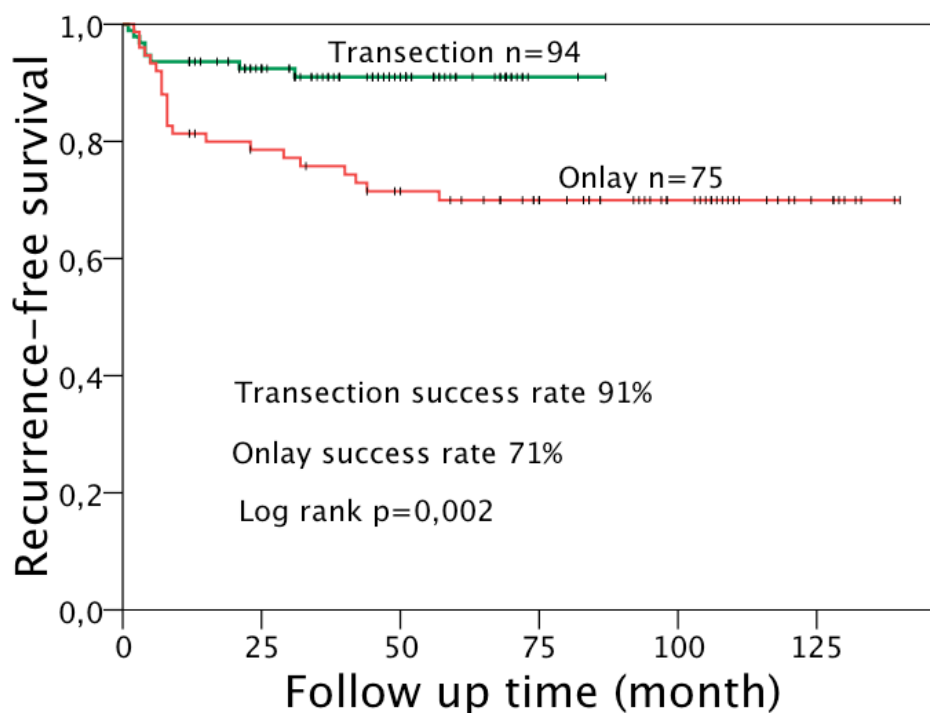
Table 1. Number of patients with postoperative sexual dysfunction.

Sexual dysfunction	SU group (N=75)	EA group (N=94)
Erectile dysfunction	1 (1%)	1 (1%)
Penile shortening/angulation	0	5 (5%)
Glans reduced filling/sensibility	0	0

Table 2. Patients who experienced sexual dysfunction post-operatively.

Patient	EA/ SU	Type of sexual dysfunction (Exact text in the charts)	Stricture length	Age Years	Urine flow (ml/s)	Failure Yes=Y/ No=N	Stricture site
1	EA	Tightness during erection, straighter erection	1.5	31	18.7	N	Distal
2	EA	Straighter erection, less ejaculate	2	37	28.3	N	Distal
3	EA	Straighter erection	2	69	10.3	N	Distal
4	EA	Shorter penis, angulated down, straighter erection	3	48	11.6	N	Proximal
5	EA	Straighter erection	0.5	49	41.5	N	Distal
6	EA	Intercourse not possible, less erection, some morning erection, Inj Caverject effect, difficulty with inj. due to body weight 147 kg	2.5	51	23	N	Proximal
7	SU	Less erection	4	74	20	Y	Distal

EA excision with anastomosis; SU substitution urethroplasty



Numbers at risk						Time (months)
0	25	50	75	100	125	
94	70	36	2			EA-transection
75	56	48	38	23	8	SU-onlay

Hazard ratio (95% CI): 1.20 (1.47–7.44)

Stratified log-rank test:  $p=0.002$

Figure 26. Kaplan-Meier curve showing the recurrence-free rates after SU and EA.

## Paper II

The penile urethroplasty groups are described in Table 1 of Paper II. The success rates were 65% and 72% for the one-stage and two-stage procedures, respectively (see Table 2 in Paper II). Age, stricture length, LS, and hypospadias were not significant risk factors for failure in either group. However, LS and age in the two-stage group showed trends towards statistical significance in the univariate analysis, both with a  $p$  value of 0.07. In both the univariate and multivariate analyses, previous urethroplasty surgery and BMI were identified as significant risk factors for recurrence in the one-stage urethroplasty group, albeit not in the two-stage group (see Table 3 below and Table 2 in paper II). After excluding the free grafts from the one-stage group, BMI still remained a significant predictor of failure (univariate analysis;  $p=0.02$ ).

Table 3. Risk factors for failure in one-stage and two-stage urethroplasty for penile stricture.

Urethroplasty type	One stage			Two stage		
	P value	OR	95% CI (low-high)	P value	OR	95% CI (low-high)
<b>Univariate analysis</b>						
Age	0,553	0,99	0,959-1,023	<b>0,078</b>	0,943	0,883-1,007
BMI*	<b>0,011</b>	1,187	1,04-1,355	0,587	1,05	0,881-1,25
BMI>30	<b>0,009</b>	5,566	1,528-20,274	0,341	2,4	0,396-14,556
Pre op/DVIU**	<b>0,015</b>	6,882	1,464-32,346	0,643	0,667	0,12-3,709
Stricture length	0,823	1,021	0,848-1,23	0,554	1,095	0,811-1,477
Hypospadi	0,187	1,941	0,725-5,195	0,245	2,708	0,504-14,541
Lichen sclerosus	0,343	1,68	0,575-4,905	<b>0,077</b>	0,13	0,014-1,249
<b>Multivaible analysis</b>						
BMI	<b>0,042</b>	1,165	1,006-1,35	0,25	1,153	0,905-1,469
Age	0,297	0,982	0,948-1,016	0,136	0,927	0,839-1,024
Lichen sclerosus	0,842	1,138	0,318-4,071	0,307	0,27	0,022-3,337
Pre OP/DVIU	<b>0,02</b>	6,717	1,354-33,321	0,424	0,404	0,044-3,728

\*BMI Body mass index

\*\*Pre op/DVIU Previous urethroplasty or/and direct vision internal urethrotomy

An odds ratio (OR) increase of 1.2 was observed for every unit increase in BMI. Considering the categorical cut-off BMI of >30, an OR of 5.6 (95% CI 1.5-20.3) with a *p*-value of 0.009 was found. The majority of the failures developed within two years (see Table 3 in paper II). The first 55 consecutive penile urethroplasties had a significant higher failure rate than the last 54 penile urethroplasties (Table 4). Twenty-six of the 36 of the failures appeared within a 2-year follow-up time (see Table 3 in paper II).

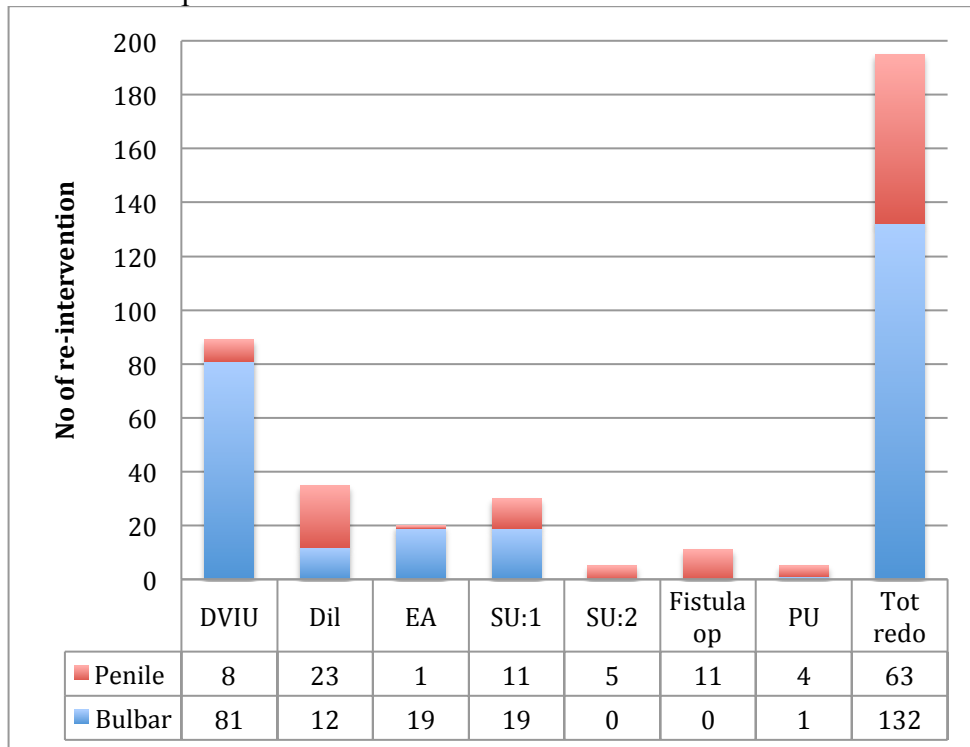
Table 4. Outcomes of the first 55 one and two-stage urethroplasties, compared to the outcomes of the last 54 urethroplasties during the period 2000-2011. (Fisher's exact test, *p*=0.002, OR=0.235, 95% CI 0.1-0.6)

n=109	First group	Second group
No Failure	29	44
Fistula	8	2
Restricture	18	8
Sum	55	54

### Paper III

The 82 patients included in this study had 2.4 re-interventions per person, corresponding to a total of 195 re-interventions together. The procedures performed were: 124 transurethral procedures (89 DVIU's and 35 dilatations); 20 EA; 30 SU:1; and 5 SU:2 (Figure 27).

Figure 27. Numbers and types of re-interventions performed in 82 patients after failed urethroplasties due to urethral strictures.



DVIU direct vision internal urethrotomy; Dil dilatation; EA excision with anastomosis; SU:1 one-stage substitution urethroplasty; SU:2 two-stage substitution urethroplasty; PU perineal urethrostomy.

Of the 195 re-interventions, 63 involved penile strictures and 132 involved bulbar strictures. In the bulbar group, all the SU:1 were free grafts, while in the penile group they all were fasciocutaneous flaps, except for one that had a free graft. For the fistula operation, the Orandi technique with fasciocutaneous flap and two-stage procedures with free grafts were performed. All the re-interventions and the numbers of success are represented in Tables 2 and 3 of Paper III. A summary of the success rates is presented in Table 5.



Table 5. Summary of success rates (%) from Tables 2 and 3.

Redo type	Success Rate	N success/ N total (%)
	Bulbar	Penile
EA	11/19 (58%)	0/1 (0%)
SU	11/19 (58%)	2/11 (18%)
SU:2	-	1/5 (20%)
DVIU	25/81 (31%)	2/8 (25%)
Dil	1/12 (8%)	4/23 (17%)
Fistula op	-	7/11 (64%)

EA excision with anastomosis; SU substitution urethroplasty; SU:2 two-stage urethroplasty; DVIU direct vision internal urethrotomy; Dil dilatation. Fistula surgery was performed with either SU or SU:2.

Table 6. Number of re-interventions after failure of urethroplasty for bulbar strictures. Numbers of cured patients indicated in parentheses.

Primary urethroplasty	Type of Re-intervention	Reop1	Reop2	Reop3	Reop4	Reop5	Reop6	Reop7	Success rate; N success/ N total
EA N=29	EA	2 (0)	4(3)	2(2)	0	1(1)	0	0	6/9 (67%)
	SU:1	1(1)	2(1)	2(2)	2(1)	1(0)	0	1(1)	6/9 (67%)
	DVIU	23(11)	9(3)	2(0)	3(0)	1(0)	2(0)	0	14/40 (35%)
	Dilation	3(0)	2(1)	3(0)	0	0	0	0	1/8 (11%)
	PU	0	0	0	0	1	0	0	End failure
SU:1 N=27	EA	1(0)	6(3)	2(1)	0	1(1)	0	0	5/10 (50%)
	SU:1	1(0)	2(2)	4(2)	1(0)	0	1(0)	1(1)	5/10 (50%)
	DVIU	23(4)	12(6)	2(0)	3(1)	1(0)	0	0	11/41 (27%)
	Dil	2(0)	1(0)	0	0	1(0)	0	0	0/4

EA excision with anastomosis; DVIU direct vision internal urethrotomy; SU:1 one-stage substitution urethroplasty; Dil dilatation; PU perineal urethrostomy.

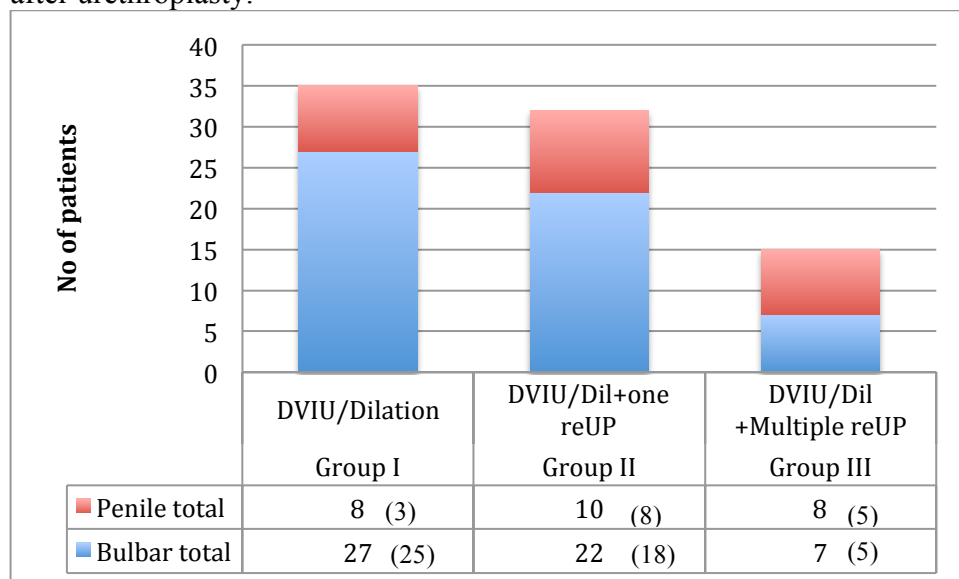
The success rates for the penile group were much lower than the bulbar group. The results for re-intervention with SU and EA were similar in the bulbar group, even though if the primary urethroplasty were EA, a higher success rate was achieved compared to primary SU, 67% to 50% (Table 6.).

DVIU had a total success rate of 30% (27/89; Table 5) with one or repeated procedures, whereas dilatation gave a low success rate of 14% (5/35; Table 5). There were long mean/median follow-up periods after the last intervention of 70/65 months (range, 6–188 months) for bulbar strictures and 82/77 months (range, 15–181 months) for penile strictures.

The cohort was divided into three treatment groups according to treatment intensity (Figure 28.). In the first group, 28 out of 82 patients (34%) experienced a successful outcome with a single or multiple endourological interventions (both dilatation and DVIU). One-fifth of the patients were cured with one DVIU (20%; 16/82; reop1; Table 2 and 3 in Paper IV) with a long recurrence-free follow-up period, mean /median of 86/88 (range, 14–188) months. In the third group, each of the 15 patients underwent multiple urethroplasties (involving penile strictures, hypospadias and with LS present in many cases) whereby three patients ended up with a PU after several failed re-interventions.

Seven patients with penile stricture had a fistula after the primary urethroplasty. Five of these patients were cured after one intervention, while two patients needed additional urethroplasties, both involving a final two-stage procedure, until a successful outcome was achieved. Despite undergoing up to seven re-interventions, 18 of the 82 patients remained as failures at the study end-point date of March 31, 2016. Nine patients ended up with lifetime CISD. PU was the ultimate remedy for five patients, all of whom expressed satisfaction with this solution. A further four patients were placed on a waiting list for a new intervention, but had not received this additional treatment by the study end-point (Figure 3 in Paper IV). The mean lead-time between redo surgeries 1 and 2, was longer from a DVIU to an urethroplasty (mean, 31; median, 12; range 2–121 months) than from a DVIU to a new DVIU (mean, 12; median, 7; range 1–56 months).

Figure 28. Intervention groups and outcomes for 82 patients with failure after urethroplasty.



The numbers of patients who obtained a successful outcome are shown in parentheses. DVIU direct vision internal urethrotomy; reUP redo urethroplasty; Dil dilatation.

### Paper IV

Amongst the 45 urethral tissue specimens obtained from patients with bulbar stricture, the degree of fibrosis varied considerably between Grade I and III (Table 8 below; Figure 2 A–F in Paper IV). In the control urethral specimens, the tissue appeared to be completely normal without any signs of fibrosis, inflammation or sclerosis (Figure 1 in Paper IV.). In eleven of the urethral specimens from the stricture patients, sclerosis was clearly noticeable (Figure 2

C–F in Paper IV). The occurrence of sclerosis was a very strong predictor of failure after EA surgery. Seven out of the eleven patients who had visible sclerosis in their resection specimens redeveloped strictures that necessitated redo surgery, whereas in the patients with no evidence of sclerosis, the surgical procedure, as a rule, yielded a satisfactory outcome. For the Grade III fibrosis, whereby eight out of thirteen affected patients had a re-stricture, there was a RR of 6.6 for requiring redo surgery (Table 7). Chronic inflammation was seen in the study specimens, containing inflammatory cells, such as lymphocytes and plasma cells, as well as germinal center formation, as shown in Figure 2A in Paper IV. The finding of inflammation in 14 patients, of which two had re-strictures, was evenly distributed across the three grades of fibrosis. The stricture aetiology was; idiopathic (70%); traumatic (17%); iatrogenic (transurethral resection of the prostate and brachytherapy for prostate cancer, 7%); previous hypospadias surgery (4%); and infection (2%). Inflammation did not emerge as a risk factor for failure (Table 7.)

Table 7. The characteristics of the patients and the P value/Relative Risk for failure after urethroplasty due to bulbar urethral stricture.

	Tot	Failure	Follow-up, Median, Months (Range)	<i>p</i> value	RR (CI95%)
No patients	46	11	21 (7-54)	-	-
Grade I	19	3	19 (9-54)	0.309	0.5 (0.1-1.8)
Grade II	13	0	18 (7-26)	**	**
Grade III	13	8	37 (15-50)	0.001*	6.6 (1.9-26.8)
Sclerosis	11	7	37 (18-50)	0.001*	5.6 (1.8-16.7)
Inflammation	14	2	22 (8-54)	0.46	0.5 (0.1-2.1)

(Fisher exact test) \* significant *p* value >0.05 \*\*No failure in this group

## DISCUSSION

### Paper I

The paradigm shift in the surgical treatment of bulbar strictures, from internal urethrotomy to open urethroplasty, is the current gold standard treatment for urethral strictures. At the time that this study was designed, there was some controversy regarding the optimal urethroplasty technique (29, 40, 50, 108, 109) and the most beneficial technique for avoiding sexual dysfunction, nevertheless, and there are still discussions about the best technique (110). The success rate in this series of excision and anastomosis was 91% and that for the onlay technique was 71%, as shown above, which tallies with previous reports (82, 111, 112). The statistical analysis revealed a significant difference between the two techniques, preferable for the EA group. However, the comparison of the two methods must be regarded as scientifically disputable, given that the onlay techniques were performed before 2005 and the majority of EA after 2005, that there was a learning curve for the surgeons, as well as the study was retrospective without any randomisation procedures.

While BM grafts (11) were used, the majority of the free grafts were penile skin (64), which is associated with a higher recurrence rate (112, 113). This might explain the lower success rate in the onlay group. Another reason might be that most of the SUs were done ventrally, which may result in sacculation leading to ejaculatory failure, post-voiding dribbling, and in turn, resticture. Currently, we use the dorsal or the lateral incision for all SUs in the bulbar strictures.

The proximal dissection in the SU technique was one of the encountered difficulties that prompted us change to the EA technique, which is easier to perform and gives better control of the lumen, in our opinion. This is also one of the reasons why we made this technique shift in 2005.

In our study, we found that five of the patients in the EA had penile angulation/shortening during erection post-operatively, with four of these strictures located distally in the bulb.

Therefore, we reserve the long bulbar strictures (>2 cm) and for speculatively, also the distally situated strictures in the bulb for treatment with the SU technique.

In the current series of patients with long-term follow-up, we found a low degree of sexual function. While other studies have reported ED in 1%–40% of patients (70, 82). However, this outcome depends on when the patients are questioned regarding sexual dysfunction. If the patients are asked 6 months post-operatively, most already recovered from ED (64-66). The fact that we presented the results from the last visit to the clinic supports our conclusion of a low rate of sexual dysfunction post-operatively after transection or non-transection urethroplasty for bulbar urethral strictures. Nevertheless, one should always inform the patient pre-operatively that sexual dysfunction might appear as a complication. One limiting factor is that we did not use validated questionnaires for measuring the sexual function. We used a subjective measurement, and it depends on how open-minded the patient is and the patients communication ability, therefore there might be some missing reports about the sexual function. In this series, the vast majority of the recurrences developed within 1.5 years after the surgery. This is why a minimum of 2 years of follow-up is required and maybe longer, when some believe that a patient with an urethroplasty performed, is a patient for lifetime.

## Paper II

The factors that lead to urethroplasty failure are poorly understood and minimal research has been conducted on this topic. In this study, failure was defined as the appearance of a new stricture or a fistula that needed surgical intervention. In the review study of Mangera et al. the definition of failure varied immensely, which might be a reason of the differences in outcomes seen in studies concerning urethroplasty (114). In 2009, Breyer et al (55) found that overweight and obese patients (BMI of 25–35) were more likely to develop recurrent strictures. One year later, he (56) concluded that strictures of > 4 cm, previous urethroplasty and internal urethrotomy were predictive of failure after urethroplasty, where the population in the study included all types of urethroplasties. In the present series, we analysed exclusively the outcomes for penile strictures, over a 12-year period, in light of potential risk factors. These strictures are complex and may be associated with previous hypospadias repair and other conditions, such as LS. The potential risk factors that were examined were: stricture length; age; body mass index (BMI); LS; hypospadias; and previous DVIU/urethroplasty; and clinical experience. The success rate for the two-stage group was higher than that for the one-stage group, in similarity to previous studies (114-120). The majority of the failures (26/36) appeared within the 2 first years postoperatively, in agreement with other studies (118, 121). Fistula formation was four times more frequent in the early phase of the study period than in the late phase, which may be explained by limited experience of the surgeons in the early

phase. This could also be explicated by using too small grafts and not using enough tissue to cover the urethra in several layers, leading to both restructure and fistula formation. There were no findings of presumed risk factors in the two-stage group. The mean follow-up time was shorter in the two-stage group, with 40 months, and in the one-stage group, 63 months, and the minimum follow-up was one year. The improved outcomes and lower sensitivity to risk factors may suggest that two-stage urethroplasty should perhaps be performed more frequently. The mean age of the patients was almost the same in the two groups; 50 years and 54 years for the one-stage and two-stage groups, respectively. As strictures are diagnosed in patients of all ages, it is important to explore how ageing affects the outcome (29, 31, 122). Age had no correlation with recurrence in this study, although such correlation has been shown in another study (123). The one-stage technique using pediculated penile skin flap, free skin and buccal mucosal grafts positioned dorsally or laterally. Five patients had their grafts sutured perineally after inverting the penis behind scrotum; this was performed in the late phase of the study period. The two surgeons learned at the beginning of the study period that a pediculated skin flap was preferable, owing to the necessity of blood supply. However, they later realised that a free graft with BM, when correctly harvested and prepared, was of value for the patient. The penile skin on the shaft of the penis is thus not affected by chordae formation and angulations of the penis, which can be devastating for the patient. Over a period of 12 years, the techniques evolved and improved, as illustrated in this study. There was a significant decrease in the failure rate when the first consecutive 55 cases were compared to the last 54 cases. Therefore, experience with urethral surgery and selecting the appropriate method is of paramount importance for success. Of the 80 one-stage procedures performed, 36 had had a previous DVIU, which may have increased the length and density of the spongiositis, making the surgery more challenging. This may explain why a previous DVIU/urethroplasty was a significant risk factor for failure in the one-stage group in the present study. It is of our belief, and others, that DVIU should be avoided for penile strictures. Obesity is a known globally important risk factor for diminished health (124). Setting a BMI cut-off of >30, resulted in a significant increase in the failure rate for the one-stage group, which held true when the 68 skin flaps alone, excluding the grafts, were assessed. An OR of 1.2 was observed for every unit increase in BMI, with an odds ratio of 5.6 (95% CI 1.5–20.3;  $p=0.009$ ) being obtained when a cut-off BMI of >30 was used. Obese patients are more difficult to operate, especially in the case of urethroplasty surgery for bulbar and membranous strictures, as there is more tissue to hold back. During the evolution of urethroplasty, it has been found that using a buccal graft for those patients who have LS improves the outcome, which is also shown in this series, although LS did not emerge as a risk factor in either group, as indicated in other studies (123, 125-127).

The two-stage procedure was performed with BM according to previous literature (128). Occasionally, the first-stage plate erodes, causing scar formation. To avoid this, the width of the graft should be 3 cm, although even then the graft can shrink. Some surgeons instruct the patient to have an erection and sexual intercourse to stretch the implanted graft, thereby inhibiting the shrinking process. However, in the two-stage group, BMI was not a risk factor for failure, which might indicate that the two-stage procedure should be performed more often in obese patients. Although the length of the stricture has previously been reported as a risk factor for failure (55, 56, 118, 123, 125, 129, 130), our study does not support such findings. This might be explained by the fact that only penile urethroplasties were analysed in the present study. It would be interesting to find out if the other studies cited above, in which long strictures were linked with failure, actually comprise any cases of penile strictures. Therefore, to the crucial factor may be the grouping of penile and bulbar urethral strictures, as there is evidence that once separated, penile strictures are more likely to recur than those in the bulbar urethra (131). The study is retrospective and the study population is small, which are

limitations. However, the strength of this study is that the patients had a stringent follow-up protocol and the same two surgeons performed all the surgical procedures.

### Paper III

Male urethral stricture occurs at a rate of 0.6–1.9% and is implicated in more than 5,000 inpatient visits annually in the US (31). Despite the high failure rates associated with DVIU and urethral dilation, they remain the most commonly performed procedures for the treatment of urethral strictures (27, 132). There is a high recurrence rate after DVIU, up to 100 % depending on the number of repetitions, also after long-term follow-up. Therefore, urethroplasty techniques have evolved over the decades and now have a much higher success rate than DVIU, even though, some recurrences exist. In this study, we analysed the frequency of recurrence and elucidated the type of re-intervention that would give the best outcome, as relevant guidelines are lacking (133, 134). The collection of data on the patients was relatively easy, in the form of a retrospective chart review. However, to present the findings candidly was difficult due to the heterogeneous nature and diversity of the data. An illustration of this is when patients had undergone one up to seven reinterventions, for example three DVI, one EA and one SU and ending up with a PU. This issue is further complicated by the fact that all the patients had these re-interventions in unique combinations. In Tables 2-3 and Figure 1 of Paper III, the re-interventions are presented in a satisfactory way, although one cannot follow each patient separately. Instead you can see the trends and the success rate for each re-intervention. The types of re-interventions are presented; 89 DVIU's; 35 dilations; 20 EA; 30 SU; 5 SU:2; 11 fistula procedures; and 5 PUs for a total of 195 re-interventions. So what did we find?

In the present series, 28 patients (from a total of 82 patients; 34%) were cured using endourological procedures, such as DVIU and dilatation, at a mean follow-up of 86 months. If one separates the DVIU's and the dilations, one-fifth of the patients with only one DVIU, had a successful outcome at a mean follow-up of 58 months. This tallies with other studies (40), although the previous studies showed shorter follow up times (135, 136). Therefore, DVIU may be a good first treatment, but only in cases of early recurrence of a short bulbar stricture; an even higher success rate is seen when the scar tissue have been removed during previous urethroplasties, especially in cases of posterior urethral stricture (137).

The mean lead-time between the initial urethroplasty and the first redo surgery was 17 months (range, 1–108) with similar intervals observed between forthcoming redo surgeries.

In this series, the redo procedures comprised as many as 89 DVIUs, which may be explained by the fact that we often perform a DVIU as a first intervention directly upon cystoscopy follow-up, during which a stricture has been identified. In turn, this affected the lead-time, which was shorter between a DVIU-DVIU than between a urethroplasty-DVIU. It is easier in our hospital to get the patient for a cystoscopic procedure than to get them to the operating room for a urethroplasty because of the long waiting lists for surgery. Therefore, additional DVIU's were performed while waiting for urethroplasty surgery, although some consider repeated endoscopic treatment inappropriate (138). In contrast, for the bulbar strictures, treatment of recurrent penile strictures gave unsatisfactory results for all the techniques used, with success rates in the range of 0%–25% (see Table 4 in Paper III). Five out of 35 dilations were successful, indicating a high failure rate, with the consequence that dilatation cannot be endorsed by others (50) or ourselves. These patients often have other conditions, such as LS, previous hypospadias repair, long stricture length and high BMI, which contribute to an increased risk of repeated failure (56, 89, 127, 139).

Some from the patients in the penile group in the present study exhibited a fistula as a failure, as explained earlier in the definition of failure, and all of these fistulas were successfully closed. However, two patients needed multiple re-interventions, and both ended up with a two-stage procedure as the final outcome. The fistulas that lead to the described failures developed mainly in the early phase of our series. We learned that careful covering of the urethra and closure with an extra subcutaneous layer are crucial in preventing fistula formation. For example, a failure with a long penile stricture that has already been grafted with penile skin, having a scarred penile shaft and with missing dartos layer will not be the ultimate state to dissect an additional pediculated skin graft from the penis. Thus, if one patient underwent an Orandi procedure and a fistula developed, it is our contention that a two-stage surgery is the preferred re-intervention. Even though with our two-stage procedures used as reinterventions, two out of five had a successful outcome, where three had a PU as an end result, indicating really bad conditions for redo surgery. In our total series of the two-stage procedures as primary urethroplasties, 8 out of 29 were failures, a success rate of 72% in line with previous studies (94, 127, 139). We have also performed stage-one twice in some patients, although not in those described above, to optimise the urethral plate when it becomes fibrotic and contractions occurs, necessitating surgery according to the literature (89). This information needs to be communicated to the patient during the decision-making process before surgery. When a patient has been suffering after a failed urethroplasty, especially when it is a long and complex stricture (and maybe previous hypospadias repair), with a high age and has multiple co-morbidities, we believe that this patient should be offered a PU in an earlier phase. An alternative solution for these patients is chronic dilatation for life, which is acceptable to some but is refused by patients who demand surgery. This leads us to another technique that nowadays is preferred in our clinic; a free dorsal BM inlay according to the Asopa technique (63).

Interestingly, we found that either SU or EA could be chosen as the redo surgery for bulbar strictures, if technically possible. Furthermore, it did not matter if the primary surgical technique was either EA or SU. However, the success rate was slightly higher in the primary EA group that had a second urethroplasty, than in the primary SU group. This can be explained by the excessive resection of fibrous tissue, and perhaps also by the shorter strictures in the EA group. In the bulbar group, a relatively high success rate (33%) was noted for a single DVIU, which decreased (27%) when multiple DVIU's are performed. The pattern for the penile group was similar, except that the number of DVIU's in this group was lower than in the bulbar group, and the fistula redo surgery showed a higher success rate (64%) than the redo surgery for strictures (19%). Therefore, in general, it is recommended that after one failed DVIU or dilatation, one should proceed with open urethroplasty for a recurrent stricture. Local administration of steroids, which are known for their anti-fibroblast and anticollagen activities, during DVIU has showed promising results, albeit in small-scale studies and with a short follow-up regimen (140), so further prospective studies are warranted. We have proposed algorithms for recurrent bulbar and penile strictures in Figure 29 and 30. Failures usually appear within the first 2 years, although some failures occur later on. It is important to consider if it is necessary for life long follow up in the complex patients, i.e., those with long strictures, with multiple redo surgery and above all, those in the penile group. There will always be patients with new recurrences, especially in the short follow-up group. Blaschko et al have suggested that repeat urethroplasty may achieve a reasonable success rate when performed by surgeons who have good success rates in primary urethroplasty cohorts (127). However, in our series (according to Tables 2 and 3), the success rate increased with repeated redo urethroplasties. For example, the success rate for urethroplasties in reop1 (6/18) was 33%, which is quite low. However, from reoperation 2 (10/19) to reoperation 3 (9/15) the success rate increased from 53% to 60%. This might be explained by the limited experience

the surgeons had at the beginning of the series, an experience previously reported by others (139, 141).

One should bear in mind that the current pattern of practice among newly certified American urologists show that only 4 % perform open urethroplasties (142).

The limitations of this study are that it is retrospective, lacks randomisation, and does not use health questionnaires for the follow-up, and incorporates the shifting in urethroplasty techniques that has occurred over the past 15 years, with potential loss of patients to follow-up, even though Sweden is a small country. Therefore, we need prospective studies that are based on an adequate follow-up regimen, and that use health questionnaires, and that integrate the information from a yet to be established registry for urethroplasties conducted in Scandinavia.

In summary, redo surgery of urethral stricture is challenging, especially in penile strictures. Nevertheless, these patients have a fair chance of success even if they require multiple re-interventions.



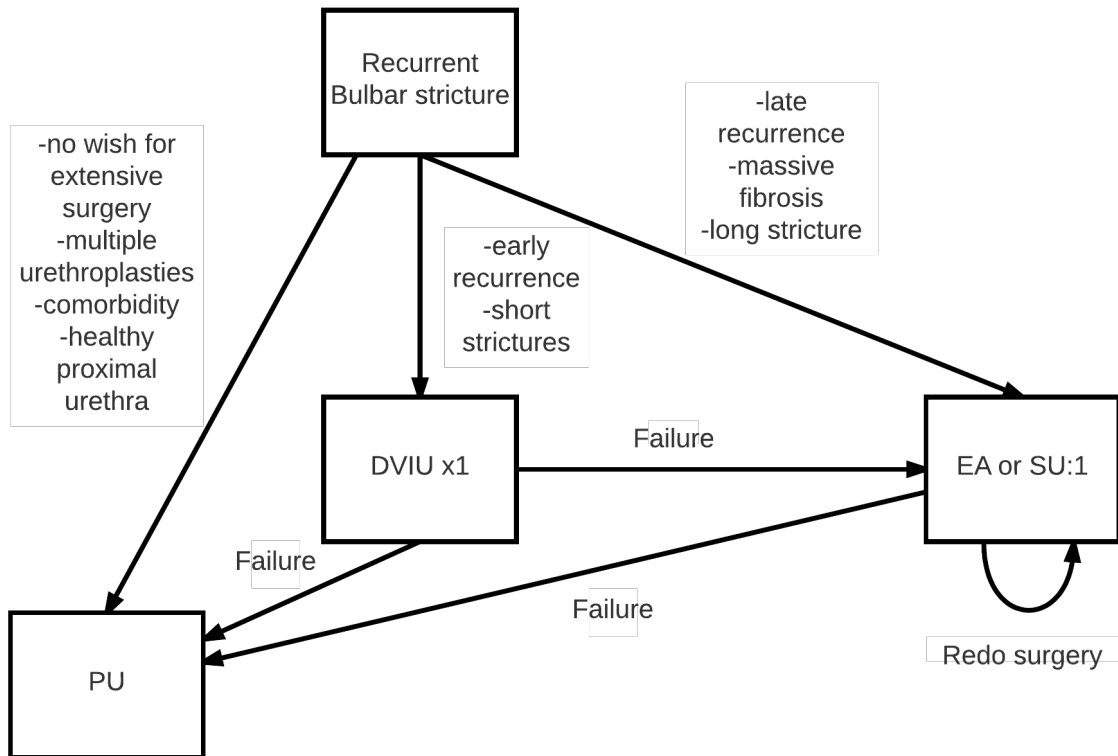


Figure 29. A proposed algorithm for re-intervention after primary urethroplasty for bulbar strictures.

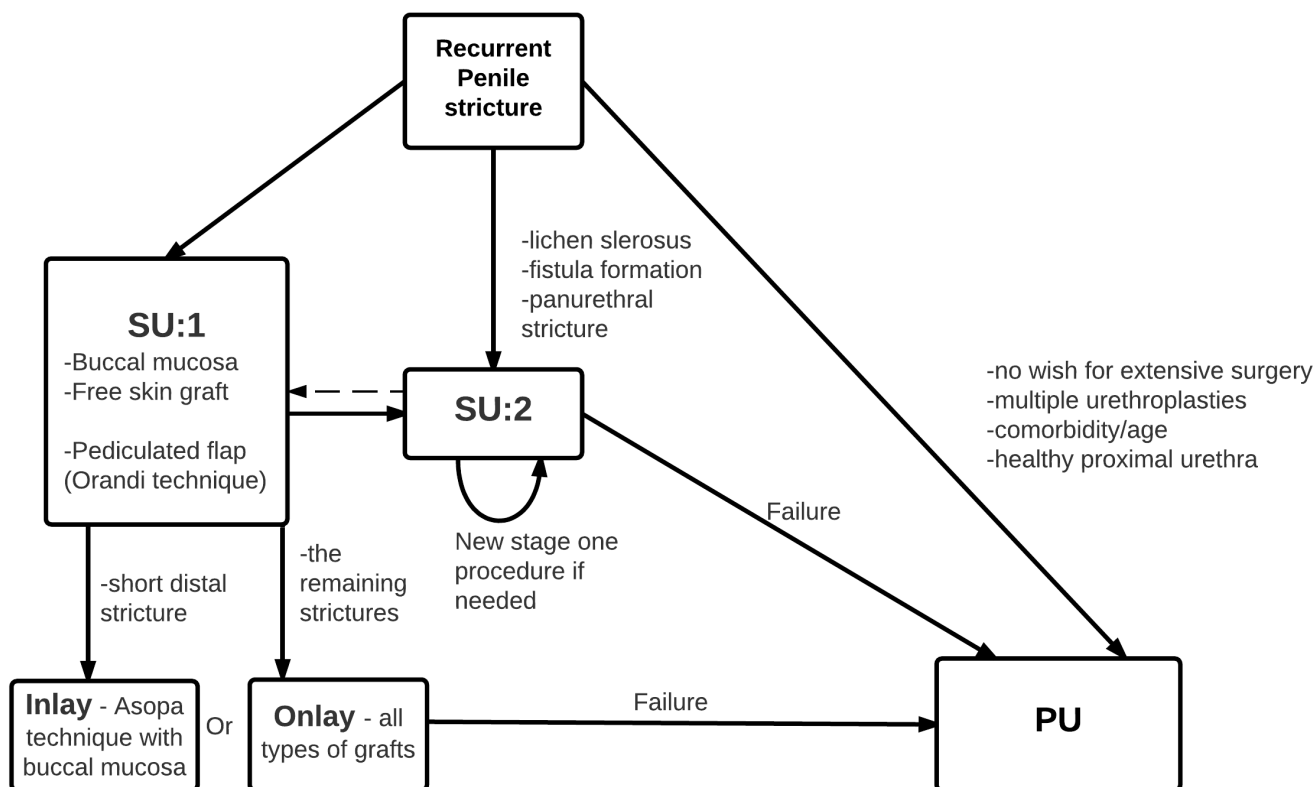


Figure 30. A proposed algorithm for reintervention after primary urethroplasty in penile strictures.

#### Paper IV

To our knowledge, there are no published studies that have analysed the pathophysiology of the excised specimens excised from bulbar stricture urethroplasties. Fibrosis has been analysed in other organs, and fibrosis have been categorised using different grading systems. In the present series, the finding of severe fibrosis, of Grade III, and sclerosis were risk factors for failure after EA for bulbar urethral stricture. Herein, the vast majority of the patients with severe fibrosis who had restructure also had sclerosis. This strengthens our contention that it is important to excise all the fibrotic tissue during the primary surgery, to diminish the risk for restructure.

The bulbar urethra is the most common location for urethral stricture and the aetiology may be idiopathic, iatrogenic, traumatic or infectious, with these types being fairly evenly distributed (143). In the present series, an idiopathic aetiology was the most common, followed by a traumatic aetiology.

There have also been attempts to classify the degrees of fibrosis using sonography and urethrography, although such classifications are operator-dependent and subjective given that compression with the probe might alter the lumen (144). We did not have a clear histological

basis or classification for the formation of the stricture and the fibrosis until the present series, in which we were able to define fibrosis according to three grades, I-III.

Fibrosis is a general feature of the healing that take place after inflammation or necrosis and it exists, for instance, in other organs, such as the lung, kidney, heart and the skin after wound healing, with these different conditions appearing to express a somewhat similar histopathological patterns (145, 146). The formed scar, leading to a urethral stricture, is dense, hypovascular and has a reduced number of elastic fibers, and also contains fibroblasts. The healing process in, for example, a inflamed wound includes the stimulation of interleukin-13, which stimulates transformal growth factor (TGF) - $\beta$ 1 production, which in turn stimulates fibroblasts to produce extracellular matrix and fibrosis. This process can be inhibited in various ways; although further studies are needed before these interventions can be implemented clinically on a large scale (147-150). Some specimens show suspicious ectopic germinal centres that might play an important role in stricture formation. These cellular and molecular events might be targeted by inhibiting or enhancing immunological pathways of lymphocytes and plasma cells, nowadays evolving research avenues (151-153). Inflammation due to LS may involve the urethra, usually only the glans, meatus, and the penile urethra, whereas the bulbar urethra as a rule is not affected by LS (154). In this study, we did not see any correlation between inflammation and the risk for restricture, with inflammation being equally involved in all the grades of fibrosis, which might indicate that inflammation plays a major role in stricture formation overall.

The present series was rather small and the follow-up times varied, which are obvious limitations. Another shortcoming is that there is no uniformly established classification concerning the severity of fibrosis. The proposed classification in the present series could perhaps facilitate future histopathological investigations of urethral stricture disease. The control specimens with normal urethra were collected from patients who had undergone sex-change surgery, where their pre-operative treatment with eostradiol might have had an affect on the urethra, although to our knowledge no evidence for this exists to support this notion. (155, 156)

The study has several important strengths, including its prospective design, the consistent follow-up regimen, and the fact that the uropathologist was blinded to the clinical outcome. The major strength of the study is that sclerosis in the specimen was a clear-cut histopathological finding agreed upon by the surgical pathologists. Thus, the specimens can be dichotomised and our clear and highly significant finding that the patients with sclerosis were strikingly over-represented when it came to the redevelopment of stricture disease, is the most important message of this study. This may also serve as a valuable tool for deciding on a suitable follow-up regimen based on the histopathological findings in the resected specimens. Moreover, in the case of restricture, knowledge of the histopathological features at primary surgery might be helpful when choosing the preferable technique to use for the redo surgery. In fact, our findings might even open up a possibility to use frozen sections during surgery in order to elucidate sclerosis involvement and extension; in the case of a finding of sclerosis in the resection margin, excision of additional tissue might be beneficial, perhaps necessitating an augmentation with SU surgery. Finally, further studies are needed to confirm whether excessive excision of the fibrosis can diminish the risk for restricture.

## METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

The same person (T.O.E) collected the data on the cohort from the charts at the Sahlgrenska University Hospital in Gothenburg, Sweden. The co-authors (L.G and K.L) performed all the surgeries and collected multiple random samples from the cohort in order to ensure that the data are accurately perceived and collected in a proper manner. Each operation was assigned a number, a key-code, such that that if an individual patient underwent several surgeries, he had several key-codes. That means that one number is not equal to one patient, but rather to one surgical event.

There are several ways of defining failure according to the literature, for example to use urinary flow or a specific chériere measurement for making a decision as to whether or not the patient needs an intervention. This means in general that a failure described in one random study concerning urethral stricture may not be a failure in another, which complicates this research area (114). In our series, we define failure when the patient is in need of surgery, such as dilatation, DVIU or a new urethroplasty, by examining the patient's symptoms and inspecting the urethra with a cystoscope.

### Paper I

In a perfect world, all studies would be prospective, randomised, and double-blinded. However, this study is retrospective and without any randomisation, which is a limitation. During this period, 1999–2009, we identified the patients, and in 2005 there was a major shift in surgical techniques from SU to EA for bulbar strictures. Thus, 58 patients of the total of 75 patients, who underwent SU, had SU performed before 2005. The majority, 91/94 who underwent EA, had EA performed after 2005. The surgeons had more experience after 2005. This is the reason why it is debatable that EA is superior to SU, even though the Kaplan-Meier curve shows significance in this respect. One could propose that the Kaplan-Meier curve should have been divided into separate curves.

In this paper 22 patients were referred from other hospitals. Hence, letters were written to these hospitals to obtain the follow-up regimens.

In the population of this study eight patients underwent two urethroplasties each, among these there was a black sheep, a patient who has key-codes in both groups and also failures in both groups. This patient had had a Bengt Johansson urethroplasty previously and had at our clinic an EA in 2008. He had a recurrence and a new procedure with a SU in 2009, in addition to three DVIU's in between these procedures. In late 2009, he ended up with a perineal urethrostomy. He epitomises the complexity of urethral stricture disease.

To improve this study, a questionnaire with items addressing micturition and sexual function should have been used before and after surgery (157-160).

Two of our patients had compartment syndrome, which did not interfere with the outcome of the urethroplasty. However, it prompted us to place this patient in a low-leg position with the feet positioned not higher than 20 cm above heart level. After this position change, there has been no further compartment syndrome.

### Paper II

In this paper, which focuses on penile strictures, 16 patients presented as referrals from other hospitals, leading to letters being sent to the referral hospitals so the follow-up regimen could be analysed. The stricture length for 22 patients were missing in the charts, but after looking

into different charts, such as radiology, operation, and cystoscopy notes the stricture length were estimated by co-author L.G. A phone call was also made to 20 patients who had less than 12 months of follow-up.

As previously explained there were 109 procedures in 90 patients. Hence, 12 patients had 2 procedures, two patients had 3 procedures, and one patient had four procedures. This sums up to 19 procedures more than patients.

To examine the outcome and possible risk factors univariate binary logistic regression was used to analyse the correlation to failure. BMI and previous urethral surgery had a significant p-value where age and lichen sclerosus had trend values, why these were analysed further on in a multivariate evaluation.

### **Paper III**

In contrast to the patients in the studies described in Papers I and II, the patients in Paper III are not presented several times. Instead, each patient has one to several re-interventions. The patients were operated on between January 1<sup>st</sup>, 1999 and (at the latest) December 31<sup>st</sup>, 2013, with the latest follow-up date being March 31<sup>st</sup>, 2016, our study end-point. In the case of two-stage urethroplasty, the second stage procedures with tubularisation were considered to be the operating date, and follow-up time was calculated from this date and to the last follow-up date.

There were 23 patients who had 0–5 months of follow-up, why a telephone call was made to these patients asking about micturition and sexual function, and the follow-up was calculated from the date of the operation to the date of the telephone call. Regarding the four patients who were awaiting for cystoscopy or re-intervention, two had their surgery done in 2016 and two are still waiting, one for a SU and the other for a PU.

### **Paper IV**

In Paper IV, the classification of fibrosis is based on examination of the 45 specimens, from 45 patients, which were revised after the primary occasion when the sample was taken. Upon re-evaluation of the specimens, the classification of the grade could be upgraded or downgraded. Fisher's exact test was used due to the small amount of patients, which is a limitation.

## GENERAL DISCUSSION AND FUTURE PERSPECTIVES

### Quality assurance and follow-up

Hopefully, in the future, the patient-reported outcome measures (PROM), ICS-Quality of Life, AUA-IPSS, and UREThRAL questionnaires will be used more extensively, so that the published data can be analysed based on the same parameters (159-162). Applying the same definitions of failure and the same scoring systems would facilitate comparisons between centres. In Sweden, we have several National Quality Registries that contain individualised data concerning patients' diagnoses, medical interventions, and outcomes after treatment, which can be used for continuous learning and research purposes, towards ensuring the best possible health-care together with the patient. Ideally, a Scandinavian registry for urethroplasty surgery and outcomes would be established that would provide a more substantial research base to improve the outcomes for our patients.

### Surgical development

In the present studies, and according to previous reports, short bulbar strictures have a 90%–98% success rate with EA carried out by expert hands. These results are so good that it at a glance seems that this procedure cannot be replaced by any other technique. Nonetheless, the non-transecting techniques, to minimise the trauma as well as augmentation techniques for longer bulbar strictures, have evolved and many urologists have adopted them. These techniques will probably be developed even further in the future. The main challenges that remain are the graft procedures and the one-stage penile urethroplasties, performed for the most complex strictures, as concluded in Paper III. In the future, the Asopa technique will probably be the preferred operation for penile strictures. Perhaps, perineal urethrostomy will be performed more extensively in the future than it is today, with the goal of eliminating the suffering of patients who are undergoing multiple re-interventions due to urethral strictures. Another category of patients, that most certainly will increase in the future, are those treated with surgery for prostate cancer, where a stricture rate of 0.5–32 % has been reported (163). There is a proposed algorithm for the management of these strictures using a surgical armamentarium that has an acceptable failure rate, considering the complexity of the condition (164). Urethroplasty of radiated induced strictures has been reported to have an acceptable success rate, although the postoperative incontinence rate is higher compared to those without radiance (165). This reflects the fact that these strictures predominate in the bulbomembranous area, which is more difficult to master surgically. Therefore, surgical tools need to be developed that facilitate the procedure, such as the Gourgette (Figure 31.) and the Capio device for example (165).

There exist some potential non-validated algorithms for urethroplasty surgery (29, 141). We need an algorithm that is designated specifically for recurrence urethroplasty to make our ways through the vast and dense forest of different strictures and surgical situations. In this thesis algorithms (Figure 29 and 30.) are proposed, but in need of further improvements.

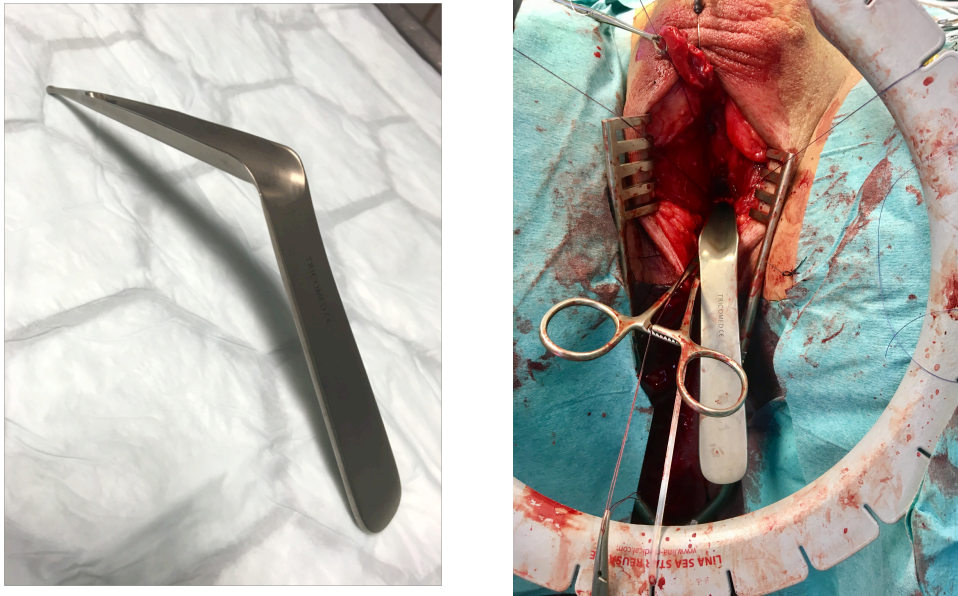


Figure 31. A gourette to open the urethra and to visualise the lumen, especially important when suturing.

### Future studies

Within the Nordic urethral stricture group (covering Norway, Sweden, Denmark and Finland) a randomized prospective multicentre study was initiated in 2015 with the purpose of analysing sexual dysfunction after bulbar urethroplasty. Three hundred patients will be needed to achieve sufficient statistical power. In the present centres, this will take 3–4 years to gather sufficient number of patients. This study will hopefully confirm, or refute, the results in Paper I.

The establishment of a Scandinavian registry for urethroplasty could give us an opportunity to investigate not only the outcome of the surgery, but also the patients and their quality of life levels in more accurate and informative ways, using a much larger cohort of patients than could be assembled if the centres acted alone.

The results of penile strictures leave a lot to be desired, why future studies are needed. For example investigating different techniques for incorporating free grafts.

In Paper IV we show that sclerosis is a predictor for failure of bulbar strictures. In the future, it may be possible to use frozen specimens perioperatively to analyse the occurrence of sclerosis.

### Tissue engineering

If buccal grafts already have been harvested bilaterally, or if the patient has a panurethral stricture with recurrence, tissue engineering has much to offer. This entails the use of various materials used that give different success rates and require different follow-up protocols (166-171). It is possible to regenerate urethral tissue, and also BM, using organic matrices as the base. In 2008, the first human series was conducted with five patients in whom autologous tissue-engineered BM was used for SU; two of the patients developed recurrence due to contracture of the graft (172). Another study that used engineered tubularised urethras for bulbar urethral strictures in five boys revealed that these urethras remained as functional as native urethras over a follow-up period of 6 years; additional studies will be needed to determine if urethral defects can be repaired in a similar way in adults (173). The main issue is to find or develop a suitable scaffold for the harvested cells, which is not an easy task and requires more clinical studies (169) (Figure 32.). One study evaluated a combined graft with

acellular bladder submucosal matrix, adding the flexibility to the mixed “graft”, and autologous urethra tissue for repair urethral stricture with a ventral onlay in an animal model with a promising outcome (174), though a short follow-up and the urethra was not confirmed functionally such as evaluation of penile angulation and sufficient elasticity to maintain erection. Therefore, to be able to produce tissue-engineered urethras in humans, we need more detailed studies that address the exact mechanisms of scar development and remodelling.

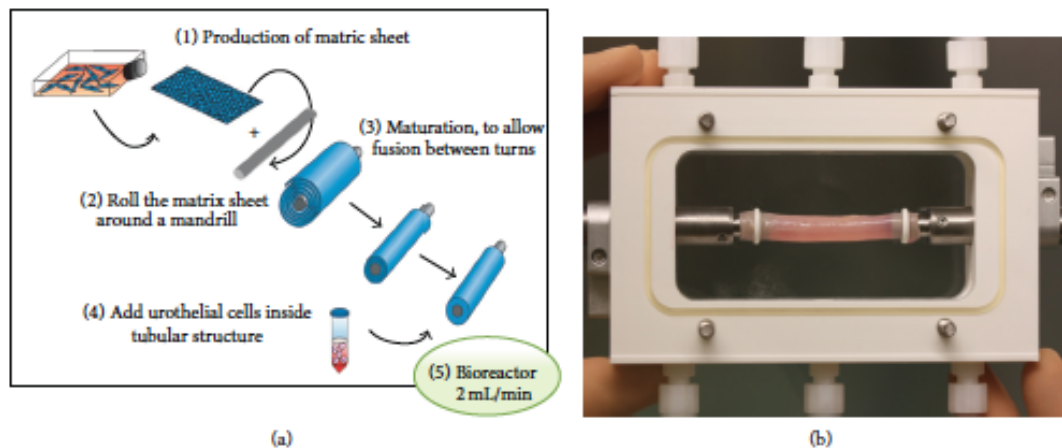


FIGURE 3: Production of cell-seeded tubular urethral graft using self-assembly technique. (a) After the production of a matrix sheet by fibroblasts, it is rolled to form a tube and urothelial cells are seeded in the lumen. (b) Bioreactor for tubular cell-seeded grafts to stimulate differentiation and formation of watertight mucosal layer.

Figure 32. Production of a cell-seeded tubular urethral graft using a self-assembly technique.

### Pharmacological treatments

It is essential for proper wound healing to have pro-inflammatory cytokines and interleukins (175) that encourage the recruitment of fibroblasts and the deposition of various types of collagen types and glycosaminoglycans (176), that promote appropriate fibrosis formation. To prevent urethral strictures and recurrences, several pharmacological agents have been used locally in animal models and also in human studies, including halofunginone coated catheters (177), intraurethral dexamethasone (149), mitomycin-C (178), rapamycin (179), metalloproteinase-1(180), TGF- $\beta$ 1(147, 150, 181, 182), and collagenase from *Clostridium histolyticum* (183), all of which have shown promising results but require further studies. Analyses of stricture formation show that it is characterised by changes in the extracellular matrix components (26), whereby the exact arrangement of the tissue of the urethral stricture is known partly at the cellular level but not at the molecular level (22, 26, 184). In other organ tissues with fibrosis and sclerosis, for example in the pancreas, lung, kidney, salivary glands, there are now new ways of targeting the diseases through the immunological pathways. This is for example characterised by increased serum immunoglobulin (Ig) G4 levels with inflammation of IgG4 positive plasma cells and with fibrotic changes in the spotted area (153, 185, 186). However, there is a need for further research on fibrosis formation in urethral strictures at the cellular, molecular and transcriptional level. If we can inhibit the formation of fibrosis, the disease might be prevented in the first place. Developing new techniques, new tools, and new bioengineered materials, and understanding the cellular mechanisms, are all essential and promising avenues for research into novel treatments for urethral strictures.



## CONCLUSIONS

### Bulbar strictures

- The excision with transection and anastomosis (EA) is a worthy method for treating bulbar strictures with a high success rate.
- There is a low risk of sexual dysfunction after either transection or non-transection urethroplasty for bulbar urethral strictures.
- To avoid penile angulation/shortening, it is advisable to use the onlay technique for longer and more distal bulbar strictures.
- A single DVIU is a reasonable first treatment for early recurrence of a short bulbar stricture.
- EA and SU are equally successful as redo surgeries for bulbar strictures.
- The presence of severe fibrosis with sclerosis in the resected specimens of bulbar strictures indicates a risk for re-stricture.

### Penile strictures

- Limited experience, high body mass index, and previous urethral surgery are risk factors for failure of open urethroplasty for penile strictures.
- Both one-stage and two-stage penile substitution urethroplasty yield success rates in line with those in previous reports.
- Penile strictures stand out as the most complex cases.

## POPULÄRVETENSKAPLIG SAMMANFATTNING (SWEDISH SUMMARY)

Urinrörsförträngning är en vanlig sjukdom. Den kännetecknas av ärrösvandlad vävnad på grund av inflammation, när urinrörets vävnad har blivit skadad på något sätt. Upphövd vattenkastning uppstår när total förträngning inträffar och patientens lidande blir då enormt. Under det senaste århundradet har behandlingarna för urinrörsförträngningar genomgått ett paradigmskifte från klyvning av förträngningen till öppen urinrörsoperation. Målet med denna avhandling var att analysera resultaten av de olika rekonstruktiva kirurgiska tekniker som använts vid Sahlgrenska Universitetssjukhuset, samt resultatet av våra reoperationer. Ett ytterligare mål var att analysera samt gradera de mikroskopiska fynden av den vävnad som bortopererats i samband med en typ av operation för urinrörsförträngningar.

Alla patienter som opererats med öppen urinrörsplastik vid Sahlgrenska Universitetssjukhuset i Göteborg mellan 1999-2014 har identifierats genom journalsystemet. Regelbundet har ett register byggts upp av en och samma person. Alla patienter hade samma uppföljningsregim efter 3, 12 och 24 månader, och längre vid behov. Om patienten var nöjd med sin vattenkastning efter två års uppföljning avslutades denna och patienten instruerades att komma tillbaka om vattenkastningsbesvären återkommer. Återfall av förträngning definierades som att patienten behövde ett nytt kirurgiskt ingrepp, såsom vidgning, en inre klyvning eller en öppen urinrörsoperation.

I artikel **I** visade det sig att i gruppen med de högt upp placerade förträngningarna, där man opererade bort förträngningen i sin helhet, hade 91 % lyckat resultat medan i gruppen där man satte in/på en ersättningsvävnad, av hud eller munslemhinna, hade 71 % lyckat resultat. En patient (1 %) i vardera gruppen utvecklade nedsatt erektionsförmåga. Operationerna för de högt upp placerade förträngningarna, visade sig således att vara mycket bra metoder vilka hade en låg grad av sexuell dysfunktion.

I artikel **II** analyserades de penila förträngningarna, varvid visades att både en- och två-steps operationer med ersättningsvävnad gav ett godtagbart resultat för vardera, 65 % respektive 72 % lyckandefrekvens, ett resultat i linje med tidigare rapporter. Tidigare genomgången urinrörsoperation samt fetma (BMI>30) var betydande riskfaktorer för återfall. Genom att jämföra de första 55 patienterna som genomgått urinrörsoperation med de sista 54 patienterna under studieperioden, kunde vi påvisa en signifikant minskning av återfall vilket tolkades som att det finns det en inlärningskurva för att utföra kirurgi av urinrörsförträngningar.

I artikel **III** identifierades 407 patienter med alla typer av förstagångs urinrörsoperationer varav 82 hade återfall med en ny förträngning och på dem utfördes 195 olika reoperationer. Båda teknikerna, antingen den med resektion av förträngningen eller den med applicerandet av ersättningsvävnad över förträngningen på urinröret, var lika framgångsrika såsom reoperation och man kan enligt vår mening välja den teknik man är mest bekväm med. De strikturer som sitter i penisskaftet har sämst utfall. I framtiden bör reoperation av återfall i den delen av urinröret som löper genom penis, som förefaller vara de mest komplicerade fallen i våra studier, centraliseras till ett högspecialiserat center för att säkerställa optimalt kliniskt utfall. En femtedel lyckades man bota bara med en klyvning, vilket kan vara en bra första behandling vid ett tidigt återkommande av en kort förträngning i övre delen av urinröret. Efter upp till sju reoperationer på vissa patienter, vid slutdatum av studien, kvarstod 18 patienter, vilkas operationer räknades som misslyckanden vid studiens slutdag. Således var 78 % botade med en lång uppföljningstid.

I artikel IV klassificerades det mikroskopiska utseendet av förträngningen hos de högt upp sittande förträngningarna i urinröret till grad I-III, där grad III innehöll skleros, vilket innebär en förhårdnad i vävnaden. Grad III med skleros visade sig vara en signifikant riskfaktor för att få en ny förträngning. Inflammation var inte en signifikant riskfaktor för återfall.

Slutsatser man kan dra av avhandlingen är att operationer av högt upp placerade förträngningar har bättre utfall än de operationer som utförs för att komma tillrätta med de förträngningar som drabbat den del av urinröret som löper genom själva penis. Det är låg risk för sexuella dysfunktioner efter såväl operationen där man skär av urinröret och tar bort förträngningen i sin helhet och den operationen med ersättningsvävnad. Liten erfarenhet, fetma och tidigare operationer på urinröret är potentiella riskfaktorer för återfall av urinrörsförträngning. Vad beträffar reoperationer så var det en relativt gott utfall, detta trots att vissa patienter genomgick flera reoperationer. Man kunde också se att val av operationsteknik, resektion eller ersättningsvävnad, inte hade någon betydelse då det blev samma utfall på de högt upp placerade förträngningarna. Förträngning med ärrvävnad av Grad III med skleros visade sig vara en signifikant riskfaktor för att få en ny förträngning. Även klassificeringen av hur fibros ser ut mikroskopiskt, enligt artikel IV, kan bana väg för utökade undersökningar ursprunget hur strikturer bildas på cellnivå, samt nya terapeutiska regimer.

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