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The management of anterior inflammatory urethral strictures

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Thesis submitted in fulfilment of the requirements of the Degree

PHILOSOPHIAE DOCTOR IN UROLOGY

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November 2017

DECLARATION OF INDEPENDENT WORK

I, Frederik Martinus Claassen, do hereby declare that this dissertation:

The management of anterior inflammatory urethral strictures

submitted to the University of the Free State for the degree *Philosophiae Doctor* is my own independent work and has not been submitted to any institution by me or any other person in fulfilment of the requirements for the attainment of any qualification.

Signed: _____ Date: _____

Principle investigator

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ABBREVIATIONS/ ACRONYMS/ SYMBOLS

AE	Adverse event
AR	Anastomotic urethroplasty
AAR	Augmented anastomotic urethroplasty with dorsal BMG
BMG	Buccal mucosa graft
cPFU	Circular pedicled penile skin flap urethroplasty
DBMGU	Dorsal onlay buccal mucosa graft urethroplasty
DVIU	Direct vision internal urethrotomy
DVIU+DIL	Direct vision internal urethrotomy combined with urethral dilatations
ECM	Extracellular matrix
MRI	Magnetic resonance imaging
PSG	Penile skin graft
PLA	Peri-luminal area
RGU	Retrograde urethrogram
SAE	Serious adverse event
UFS	University of the Free State
USD	Urethral stricture disease
VBMGU	Ventral onlay buccal mucosa graft urethroplasty

IMPORTANT DEFINITIONS

Anastomotic urethroplasty	Refers to when the narrow urethral segment is excised with the spongiosus and the healthy ends are approximated (Santucci <i>et al.</i> , 2002).
Anterior urethra	Refers to the part of the urethra from the meatal opening to the proximal bulbar urethra (Orlandini <i>et al.</i> , 1998).
Augmented anastomotic urethroplasty	The worst part of the urethral narrowing is excised. The urethra is then anastomosed ventrally or dorsally and the contralateral side is then closed with a graft (Hoy <i>et al.</i> , 2013).
Bulbar urethra	This part of the urethra extends from the penile urethra to the membranous urethra (Orlandini <i>et al.</i> , 1998).
Direct vision internal urethrotomy	Refers to an incision made endoscopically in the urethral epithelium (Heyns <i>et al.</i> , 1998).
BMG only urethroplasty	The lumen of the urethral narrowing is enlarged by performing a dorsal or ventral stricturotomy and closing the stricturotomy area with a graft (Barbagli <i>et al.</i> , 1995).
Flap	Refers to a tissue transfer where healthy penile skin is harvested with its vascular pedicle and used for urethroplasty (Whitson <i>et al.</i> , 2008)
Graft	This refers to a tissue graft without its own blood supply being transferred from one place to another, e.g. buccal mucosa is harvested from the mouth and transplanted onto the urethra (Whitson <i>et al.</i> , 2008).
Latrogenic urethral stricture	Urethral stricture caused by instrumentation such as cystoscopy. Mechanism of stricture formation is possible by pressure necrosis of the urethral epithelium. This can also be caused by indwelling urethral catheters (Latini <i>et al.</i> , 2014).
Panurethral	This refers to urethral strictures low grade involving the complete anterior urethra. The stenotic segment, which decreased the urethral lumen by more than 50% will be measured as the length in a panurethral stricture (Waxman <i>et al.</i> , 2006).
Penile urethra	It extends from the urethral meatus to the distal edge of the bulbospongiosus muscle (Orlandini <i>et al.</i> , 1998).

Peno-bulbar urethra	Urethral strictures in this part of the urethra extend from the distal bulbar urethra into the proximal penile urethra (Orlandini <i>et al.</i> , 1998).
Post-infective urethral strictures	Recurrent gonococcal urethritis as a major cause of urethral stricture disease in the developing world. The mechanism remains unclear (Lumen <i>et al.</i> , 2009).
Substitution urethroplasty with circular pedicled penile skin flap	The complete urethra is excised and replaced with a tubularised penile skin flap (Palminteri <i>et al.</i> , 2002).
Trauma related urethral stricture	This is due to external trauma to the urethra, which may be blunt or penetrating (Lumen <i>et al.</i> , 2009).
Urethral dilatation	This refers to the stretching of the stricture with a urethral dilator (Heyns <i>et al.</i> , 1998).
Urethral stricture	It is an abnormal narrowing of the urethral lumen in any segment of the urethra surrounded by corpus spongiosum (Latini <i>et al.</i> , 2014).
Urethral stricture disease	This term implies and refer to the underlying aetiology (Latini <i>et al.</i> , 2014).

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Chapter 1

EXECUTIVE SUMMARY

Introduction: Inflammatory urethral stricture disease secondary to gonococcal urethritis is a major problem among male patients presenting with urethral strictures at urology clinics in central South Africa. The incidence of gonococcal urethritis is reported as being as high as 68% by the health authorities in central South Africa. These patients present with a variety of clinical scenarios, which vary between difficulty in voiding to necrotising fasciitis, which can be fatal. The exact incidence of urethral stricture disease is not known in the general population of central South Africa. The incidence of infective gonococcal related urethral strictures presents in 81% of patients with urethral strictures visiting the urology clinic. Patients often present with palpable urethral fibrosis and diseased perineum, which increase the risk for treatment failures. Literature regarding the treatment of infective urethral strictures is exceedingly limited. The literature reports typically focus on traumatic and iatrogenic urethral strictures. An additional hindrance, which makes research challenging, is the complexity of the anterior male urethra, which differs throughout its length in urethral lumen diameter and spongiosum thickness. Follow-up that exceeds five to ten years is necessary to determine the success rates of procedures because procedures do deteriorate over time. The necessity for long term follow-up made this research demanding and data of patients with urethral stricture disease who were treated at the Universitas Academic Hospital between 2005 and 2010 were collected. No existing database existed for these patients, hence the clinic files, radiology reports and the hospital records regarding the patients' visits were collected and analysed. Procedure failure was defined as when the patient presented with symptoms suggestive of stricture recurrence, which necessitated a secondary procedure to treat the stricture.

The primary aim of this research was to develop a treatment protocol for infective urethral strictures, which can be implemented at the teaching hospitals in central South Africa. The secondary objective was to determine the long term success rates of the different procedures used to treat urethral strictures. The third objective was to modify the

anastomotic urethroplasty in order to remove the urethral catheter the following day, thus limiting the risk of catheter related stricture formation. The final objective was to determine the feasibility of incorporating the fibrotic urethra, rather than excising it as a two-stage procedure in patients with obliterated panurethral strictures.

Methodology: Databases were created from the patient folders. This was used to do two retrospective analyses on patients who had a follow-up of four to seven years. The first retrospective cohort included 308 patients with a follow up of seven years. The second retrospective study included 326 patients with infective strictures with a minimum follow-up of four years. Two prospective studies were done. The first prospective study was with thirty-six patients. A randomised control trial comparing the double layer continuous running suture re-anastomosis with the interrupted suture re-anastomosis when doing an anastomotic urethroplasty. The second prospective study was a case series of seven patients where the fibrotic urethra was incorporated in the repair of pan-urethral strictures with obliterated lumens as a two-stage procedure.

Results: The overall treatment success rates of infective urethral strictures were significantly lower than that of trauma related strictures. The stricture recurrence rate was 2.6 times higher in patients with infective strictures compared to patients with trauma related strictures. Infective urethral strictures were significantly longer than trauma related urethral strictures, mean lengths 2.3 cm versus 1.5 cm. Stricture length was the most significant cause for failure, with stricture lengths of in excess of 3.0 cm being a major risk factor and a reason for failure. Stricture location and oblitative urethral lumens did not affect the success rates of urethroplasty procedures. The seven-year success rate of the dorsal buccal mucosa onlay urethroplasty was 65%, being significantly higher than that of the 27% success rate of ventral buccal mucosa onlay urethroplasty in patients treated during this study. Urethral dilatation after direct vision internal urethrotomy was not beneficial in infective strictures but the time to stricture recurrence was longer compared to patients who had had direct vision internal urethrotomy only. The one-stage circular penile skin flap urethroplasty with a five-year success rate of 8% was considerably lower than the two-stage urethroplasty, where the fibrotic urethra was incorporated in the repair and showed a success rate of 71% in patients with infective urethral strictures. This research demonstrated that the urethral catheter can be removed twenty-four hours after

anastomotic urethroplasty performed with a double layer continuous running suture anastomosis. The double layer continuous running suture re-anastomosis had a success rate of 90%, clinically significantly higher than the 71% success rate of the interrupted suture re-anastomosis.

Conclusions: The findings of this research led to and support the following recommendations. In cases where substitution urethroplasty with buccal mucosa graft is done for strictures, the graft must be placed dorsal and not ventral. A two-stage urethroplasty combining the dorsal buccal mucosa onlay with a ventral fasciocutaneous penile skin flap is the most suitable approach for the treatment of panurethral strictures in patients with infective urethral stricture. Urethral dilatation after direct vision internal urethrotomy adds no benefit to the treatment of infective urethral strictures. The double layer continuous running suture anastomosis after stricture excision ensures early removal of the urethral catheter, thus avoiding catheter related complications. A stricture treatment algorithm for infective urethral strictures was developed from this research, centered on stricture length.

Chapter 2

LITERATURE REVIEW

2.1 Introduction

The true incidence of urethral stricture disease in central South Africa is unknown due to unreliable and in most cases, a complete lack of data. Urethral stricture disease in central South Africa has a significant debilitating impact on the quality of life of patients. Due to long waiting lists at hospitals to treat patients, they have to wear suprapubic catheters for extended periods of time with significant morbidity and an adverse impact on the manual work these patients often perform. In central South Africa the unemployment rate is 39.4% (Statistics South Africa Quarterly Labour Force Survey, Quarter 1, 2016). For an already impoverished patient the loss of income has a significant personal impact both socially and economically.

Urethral stricture disease differs between developed and developing countries. The main causes of urethral stricture disease in the developed countries are idiopathic and iatrogenic, whereas in South Africa the main cause of urethral stricture disease is gonococcal infection (Heyns *et al.*, 2012).

There are numerous questions regarding inflammatory urethral stricture disease that still need to be answered and these await further research. These questions include the incidence of strictures and how strictures differ in the different sites in terms of aetiology, length and patient age. Inflammatory urethral stricture impact on treatment, stricture site and length need to be studied and documented due to the scarcity of information. To some extent, currently there exist some guidelines with different levels of evidence for traumatic and iatrogenic strictures, but none for infective urethral strictures. A treatment algorithm for infective urethral strictures, based on stricture length and location will be most beneficial, since it will not only limit the number of procedures performed on patients, but they will also receive appropriate treatment.

2.2 Literature study and scientific rationale

2.2.1 Aetiology

In South Africa, the main cause of urethral strictures is urethritis. In fact, 45% of urethral strictures are caused by urethritis (Heyns *et al.*, 2012). *Neisseria Gonorrhoea* is the most common sexually transmitted disease (STI) diagnosed at South African clinics, with an incidence rate that varies between 36% to 68%. Binge drinking, the general acceptance by the culture of one night stands, the impunity with which couples have multiple partners and prostitution are cited as major contributors to an increase in STIs (Free State Annual Progress Report 2014/15 Provincial strategic plan 2012-2016). This is mainly why gonococcal urethritis remains a major cause of urethral stricture disease (USD) in South Africa, in contrast to developed countries where the causes of USD are instrumentation (32%), idiopathic (23%), urethral catheters (13%), trauma (3%) and infection (3%) (Lumen *et al.*, 2009). The pathological process of how *Neisseria Gonorrhoea* causes urethral strictures remains unclear (Lumen *et al.*, 2009).

The location of the stricture in the anterior urethra may be influenced by the aetiology. Inflammatory urethral strictures are usually located in the penile urethra (Fenton *et al.*, 2005), whereas idiopathic stricture is located in the bulbar urethra (Lumen *et al.*, 2009). Urethral strictures caused by instrumentation or catheterisation are typically located at the penobulbar junction (Latini *et al.*, 2014). Catheterisation may cause pressure necrosis of the urethral epithelium as well as chronic inflammation, resulting in urethral stricture formation (Latini *et al.*, 2014). Aetiology may influence treatment outcomes where post-infective urethral strictures were identified as a definite risk for treatment failure (Mathur *et al.*, 2014).

2.3 Anatomy of the male urethra

The male urethra is a heterogeneous organ, which differs in lumen diameter and spongiosum thickness. The anterior urethra is divided in the bulbar urethra, which is enclosed by the bulbospongiosus muscle and the penile urethra and runs from the distal margin of the bulbospongiosus muscle to the fossa navicularis (Figure 2.1) (Orlandini *et al.*, 1998). The bulbar urethra is rich in blood supply through the bulbar arteries that directly supply the proximal corpus spongiosum. The dorsal penile arteries supply the spongiosum with retrograde flow via the glands. Additional blood supply comes from the

circumflex branches of the dorsal arteries that run dorsal and ventral in Buck's fascia, perforating the vessels traversing the corpora cavernosum (Figure 2.2). The rich blood supply and thick spongiosum of the bulbar urethra make the excision and primary anastomosis urethroplasty a favourable technique in this location (Orlandini *et al.*, 1998). The penile urethra has a much thinner spongiosum compared to that of the bulbar urethra. The thin corpora spongiosum surrounding the penile urethra provides less optimal support for grafts and therefore substitution urethroplasty is performed with fasciocutaneous flaps (Figure 2.1). These fasciocutaneous flaps bring with it its own blood supply and can be placed ventral on the penile urethra (Andrich *et al.*, 2012).

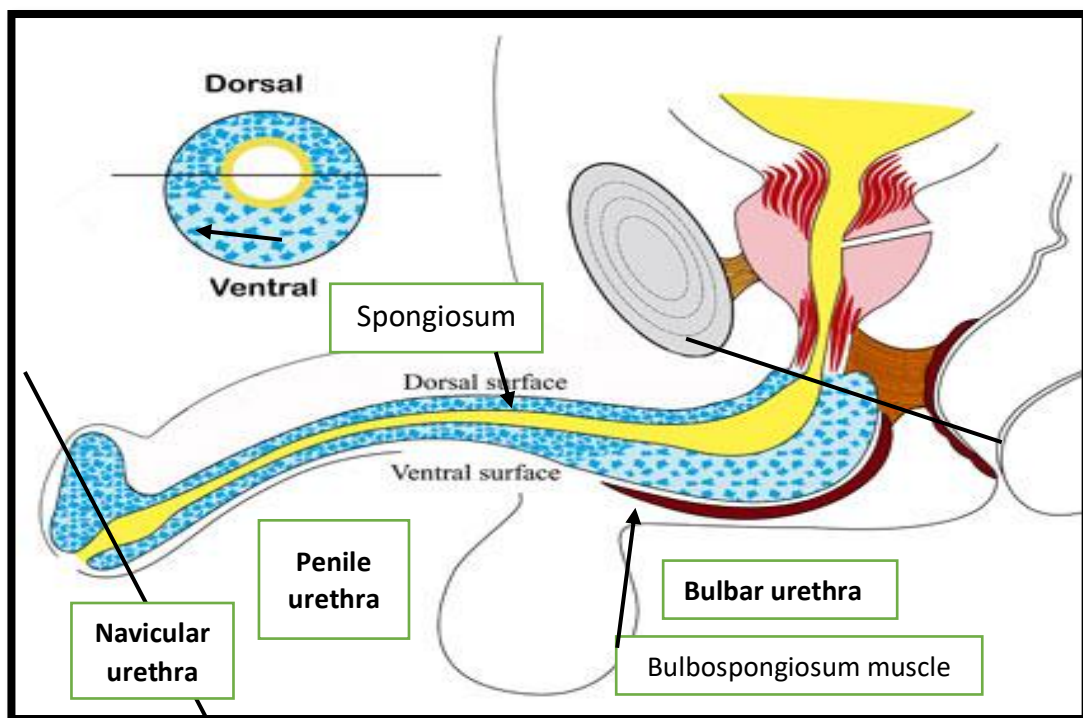


Figure 2.1. A diagrammatic illustration of the difference in spongiosum thickness in the different locations of the male urethra.

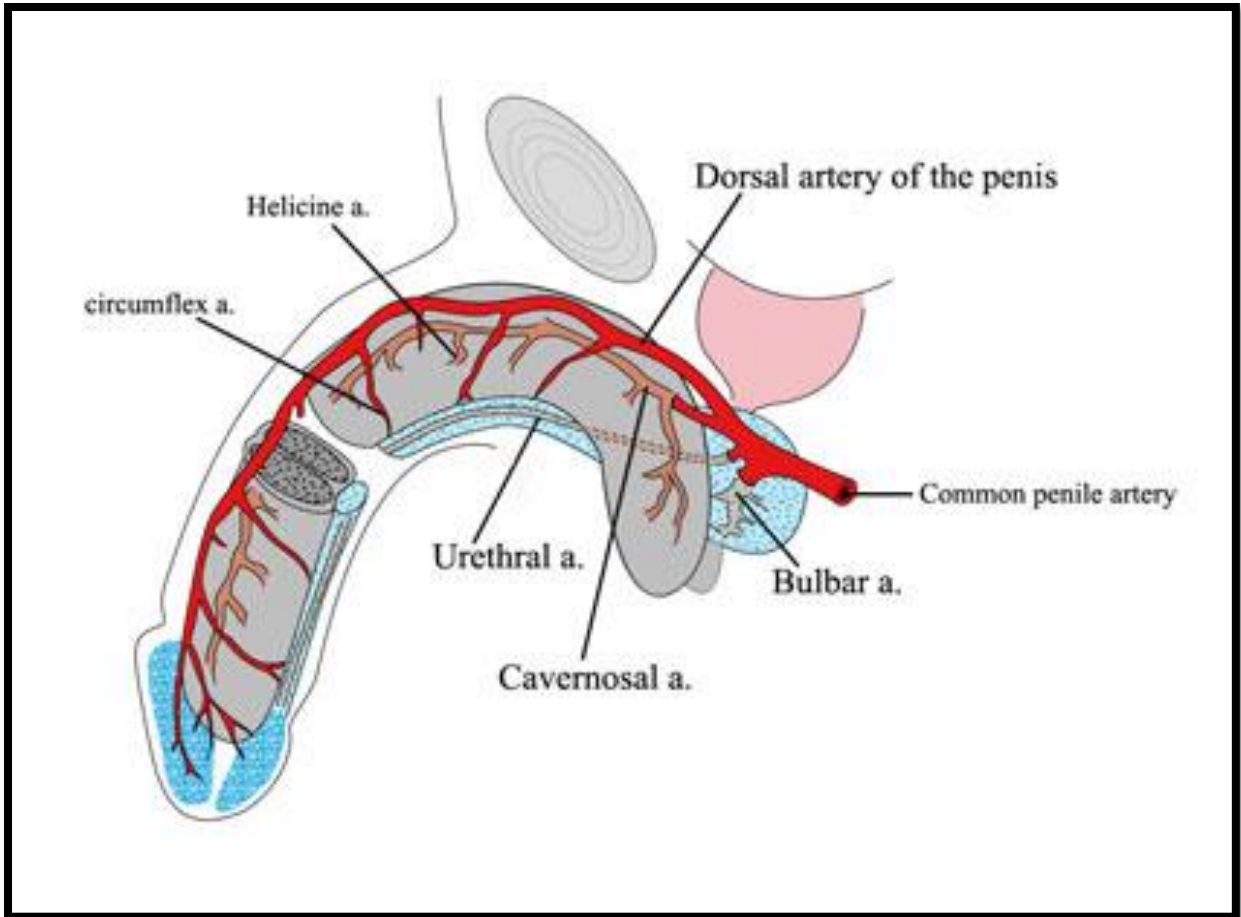


Figure 2.2. The blood supply of the penis and urethra.

2.4 Ultrastructure of urethral strictures

The epithelium lining of the human male urethra has regional differences with squamous cell epithelium in the penile and bulbar urethra. In the proximal bulbar urethra, the epithelium changes to transitional cell epithelium, which lines the posterior urethra (Orlandini *et al.*, 1989). Beneath the urethral epithelium lies the peri-luminal area (PLA), which consists of the basement membrane and extracellular matrix (ECM). The ECM consists of layers of connective tissue, vascular sinusoids of the corpus spongiosum, smooth muscle fibres and numerous mucous glands (Cavalcanti *et al.*, 2007). The ECM that is influenced by Glycosaminoglycans (GAGs) is the major cause for urethral stricture formation. Glycosaminoglycans (GAGs) are heteropolysaccharide chains composed of disaccharide repeating units. GAGs are covalently linked to a protein, forming proteoglycans, which are important components of the cell surface and ECM. (Lozzo, 1998). Glycosaminoglycans (GAGs) on the cell surfaces enhance wound healing by forming proteoglycans, which are components of the cell surface and ECM. (Cavalcanti

et al., 2007). Individual proteoglycans interact specifically with other matrix components, such as collagen or growth factors. An altered proteolytic balance of proteoglycans favours the accumulation of collagen in the ECM, resulting in a decrease in tissue compliance. (Scott *et al.*, 1996). A decrease in compliance resulting from wound healing may determine the calibre of the urethral lumen and severity of the obstruction (Oksala *et al.*, 1995). The overall increased collagen in the ECM is not the major cause of the urethral stricture but rather it is the subtype ratio change of collagen type I and type III (Cavalcanti *et al.*, 2007). Furthermore, a decrease in the concentration of hyaluronic acid and total GAGs in the urethral stricture as well as the high total collagen content may account for the undesirable biomechanical properties of urethral scar tissue.

2.5 Definition of a urethral stricture

Urethral stricture implies anterior urethral disease, which is an ischemic fibrosis of the corpora spongiosum. It results in scar tissue formation, which contracts over time, resulting in the narrowing of the urethral lumen that renders the act of urination difficult or impossible (figure 2.3a and b). Urinary obstructive voiding symptoms occur only when the urethral diameter is less than 10Fr. This is reflected in a maximum flow rate (Q-max) of less than 15 ml/s with uroflowmetry (Sing *et al.*, 2009). Uroflowmetry is a simple, noninvasive method to evaluate voiding function in patients experiencing lower urinary tract symptoms. Q-max less than 15 ml/s is used by researchers as a cut off value to predict obstruction (Heyns *et al.*, 2002). The problem when using Q-max is that other underlying pathology, such as benign prostatic hyperplasia may cause a decrease in Q-max and not necessarily a urethral stricture. Q-max of less than 15 ml/s is more sensitive to diagnose urine outflow obstruction in patients younger than forty years. It is important to note that the length of the urethral stricture might not correspond directly with the length of the spongiofibrosis. Fibrosis from the urethral stricture may extend into the corpora spongiosum and periurethral area (Figure 2.3c).

Urethral “stricture disease” (USD) is the term that underlies the aetiology, such as the inflammatory urethral stricture disease secondary to infection (Latini *et al.*, 2014).

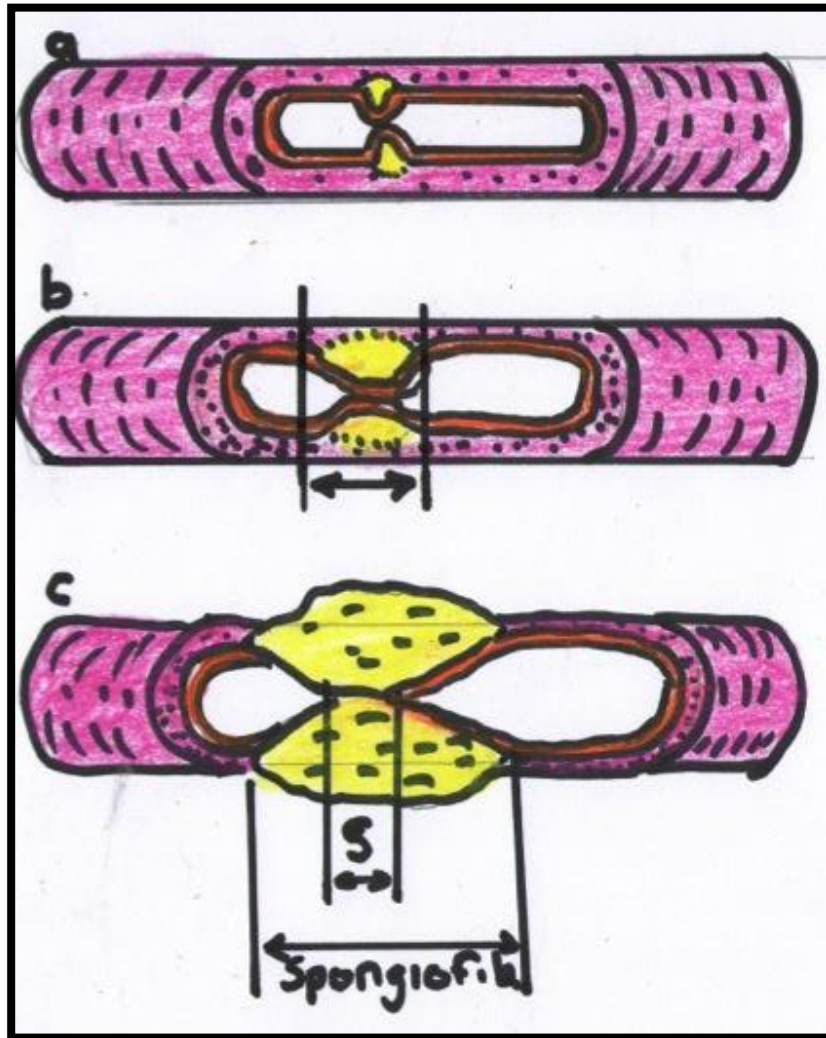


Figure 2.3. Urethral stricture: **a)** Short stricture with little spongiofibrosis. **b)** A short stricture, which can be excised. **(c)** A longer stricture amendable with substitution urethroplasty and note that stricture length(s) do not correlate with the extent of fibrosis. The spongiofibrosis may involve the peri-urethral area.

2.6 Clinical presentation and ultrastructure of infective urethral strictures in Central South Africa

According to the urethral stricture database, patients at the Universitas Academic Hospital Complex (UAHC) presented mainly with inflammatory urethral strictures secondary to urethritis. This was the cause of urethral stricture disease in 326 (81%) of 401 patients. The 326 patients had a positive history of purulent urethral discharge and according to their hospital records they received treatment for gonococcal urethritis. Patients with infective urethral strictures often present with diseased perinea and have palpable fibrosis

(Figure 2.4). There are also patients with urethral loss, secondary to perineum sepsis (Figure 2.5). In patients with complex urethral strictures, the scrotum or penile skin is often scarred and of poor quality, which cannot be used for any type of urethroplasty (Figure 2.6).

2.6.1 Diseased perineum in patients with infective urethral strictures

The various diseased perinea caused by urethral strictures that patients present with are illustrated in figures 2.4, 2.5 and 2.6.

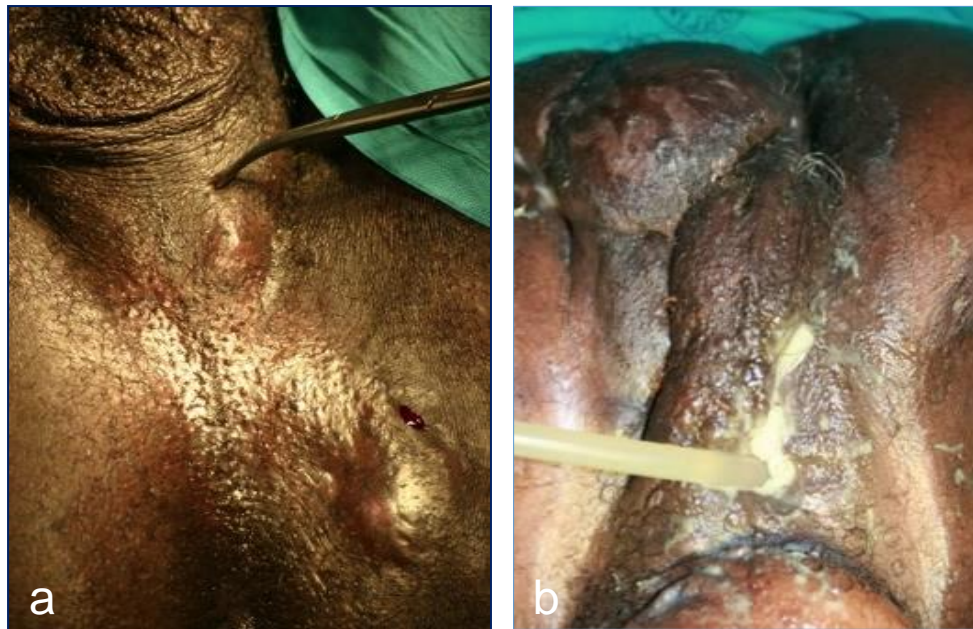


Figure 2.4. Patient with urethrocutaneous fistula and previous periurethral infection (a). Patient presented with perineum sepsis and a perineum urethrostomy was done for complete obliterated peno-bulbar and penile urethral strictures (b).

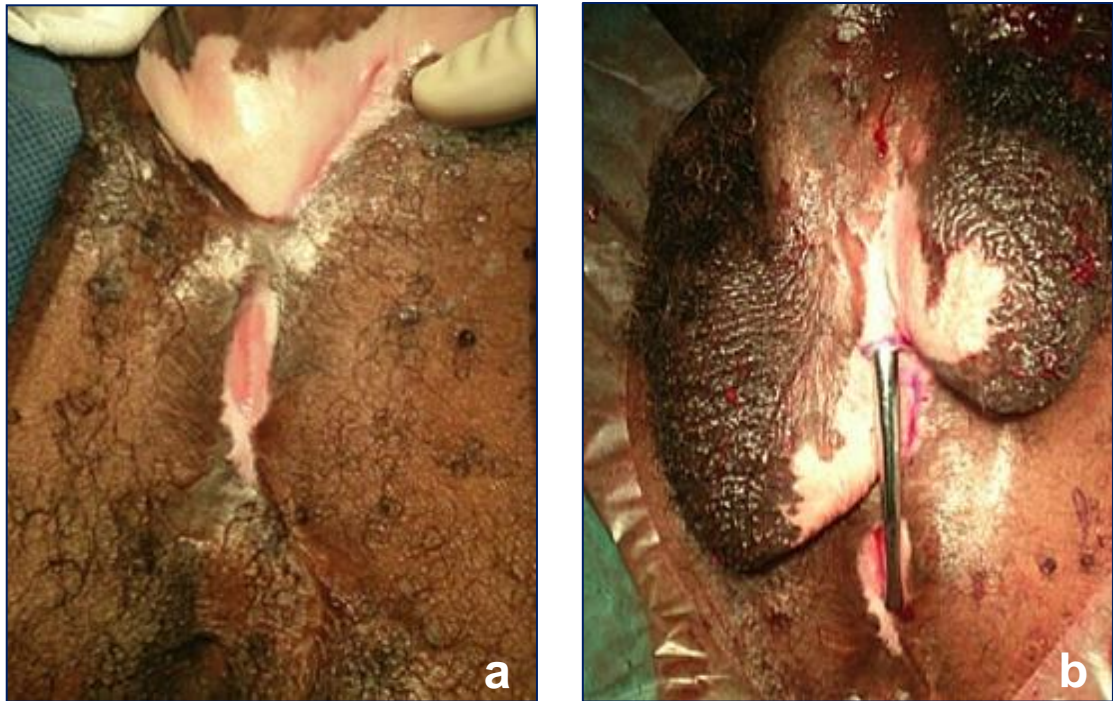


Figure 2.5. (a) Patient with urethral loss that presented initially with necrotising fasciitis and displayed complete bulbar urethral loss before reconstruction. (b) Lister dilator passed illustrates the urethral loss.



Figure 2.6. Scarring and fistulae of the scrotum and perineum.

2.6.2 Urethragrams of patients with infective urethral strictures

Retrograde urethragrams (RUG) are the only diagnostic modality available in central South Africa. Infective strictures can be complex, presenting with urethra-cutaneous or recto-urethral fistula secondary to an obliterated urethral lumen (Figure 2.7). The symptomatic narrowing may be short but the entire urethra is affected by infection (Figure 2.7).

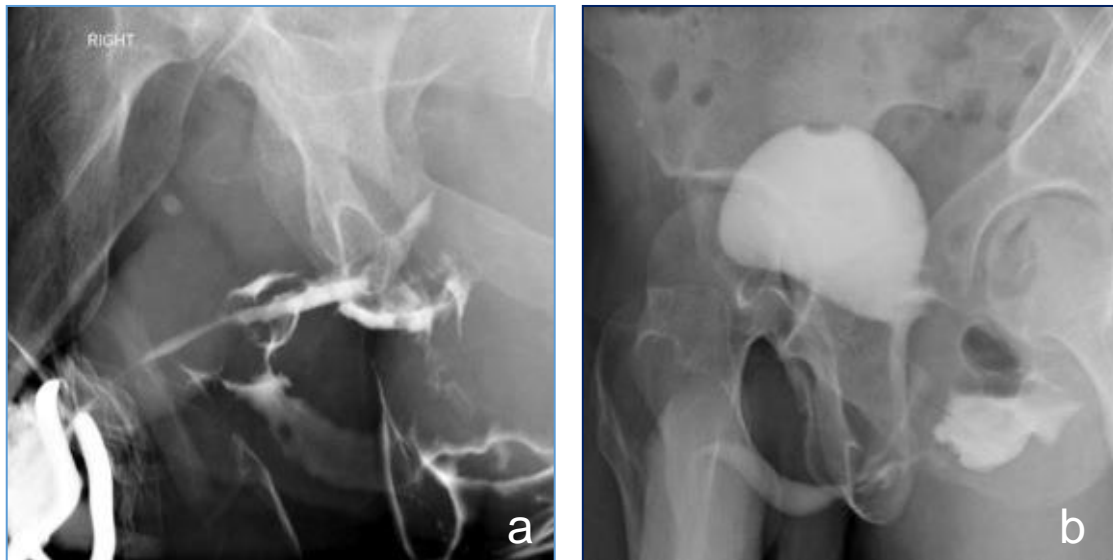


Figure 2.7. Obliterative urethral lumen with urethra-cutaneous fistula **(a)**. Recto-urethral fistula with proximal bulbar urethral stricture **(b)**.

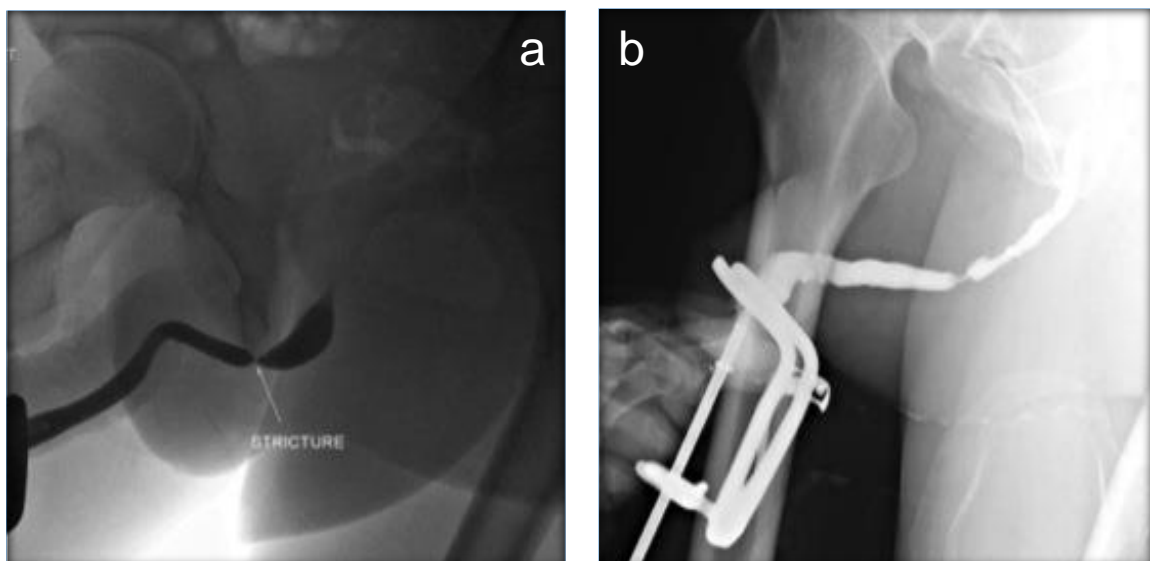


Figure 2.8. The difference between a 1 cm traumatic urethral stricture **(a)** and a 1 cm obliterative urethral narrowing in a pan-urethral stricture **(b)**.

2.6.3 The histological characteristics of infective urethral strictures

Microscopic examination of sections of the resected urethral stricture of a patient that had undergone an anastomotic urethroplasty is illustrated in (Figures 2.9 to 2.15). The urethral lumen shows marked stenosis (narrowing), filled with luminal debris and calcified material. A focus of complete luminal obliteration is also present (Figure 2.10). The epithelium is attenuated but intact and the disease process has affected the subepithelial layer and the spongiosum (Figure 2.9). Upon low-power view, the resected urethral segment shows expansion of the subepithelial connective tissue compartment by a dense fibro-inflammatory reaction, which effaces the inner part of the corpus spongiosum (Figure 2.9). The subepithelial layer consists of granulation tissue with proliferation of capillary vessels and reactive fibroblasts (Figure. 2.11). A background of severe chronic inflammation is noted, featuring an infiltrate of lymphocytes and plasma cells, with focal lymphoid follicle formation (Figures 2.12 and 2.13). Dense fibrosis surrounds the granulation tissue and this partly effaces the inner compartment of the corpus spongiosum (Figure 2.13). Several of the small arterial vessels in this region show endarteritis obliterans (Figure 2.14). The dense fibrosis of the subepithelial area and spongiosum may negatively influence substitution urethroplasty. The spongiosum with fibrosis and poor blood supply might not be suitable for graft inlay or onlay types of urethroplasty.

Microscopic examination of sections of the resected distal urethral segment, as well as of the normal-appearing segment, shows less pronounced and more superficial chronic inflammation and fibrosis of the subepithelial connective tissue, with patency of the urethral lumen (Figure 2.15). The fibrosis present in the normal appearing urethra illustrates how easy it will be to underestimate the true length of an infective stricture.

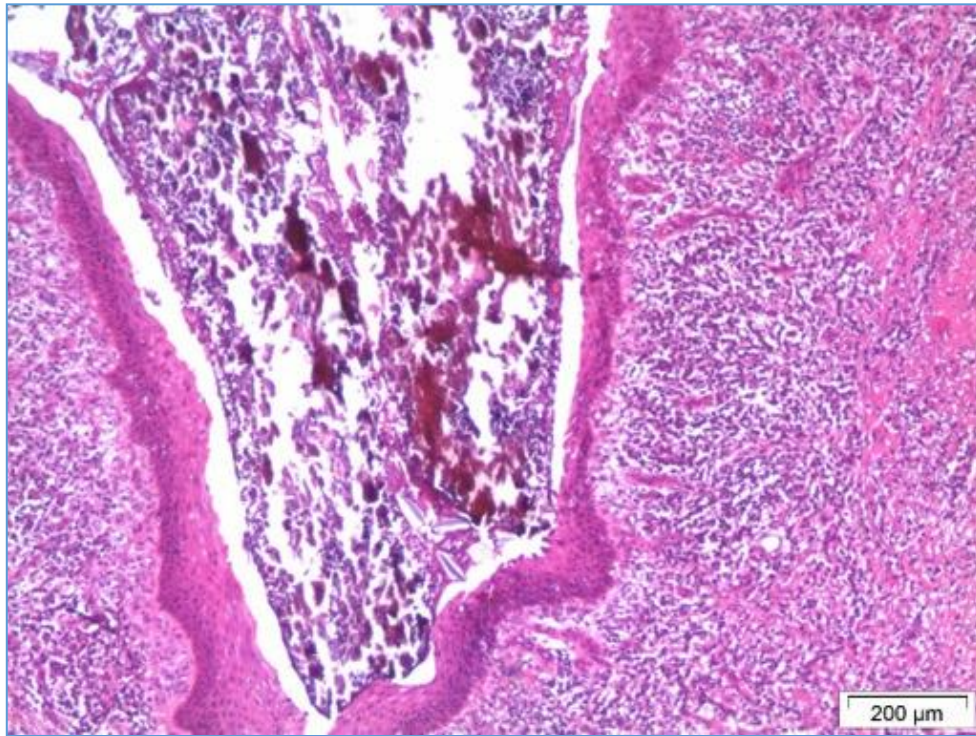


Figure 2.9. A fibro-inflammatory reaction, which affects the inner part of the corpus spongiosum with attenuated squamous mucosa.

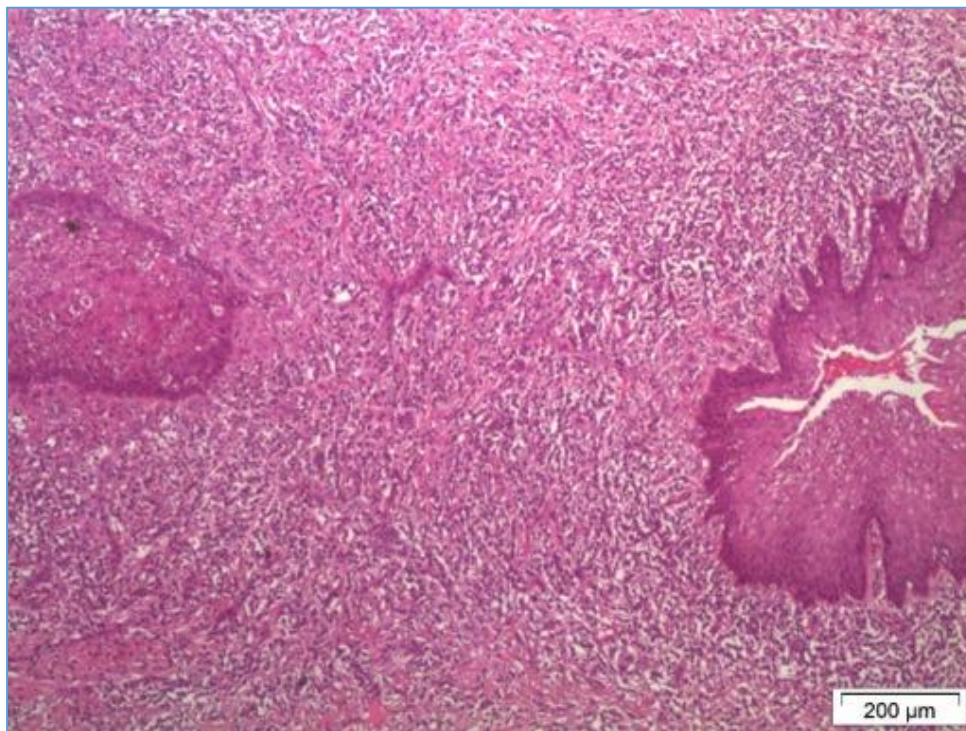


Figure 2.10. A focus of a near obliterated lumen.

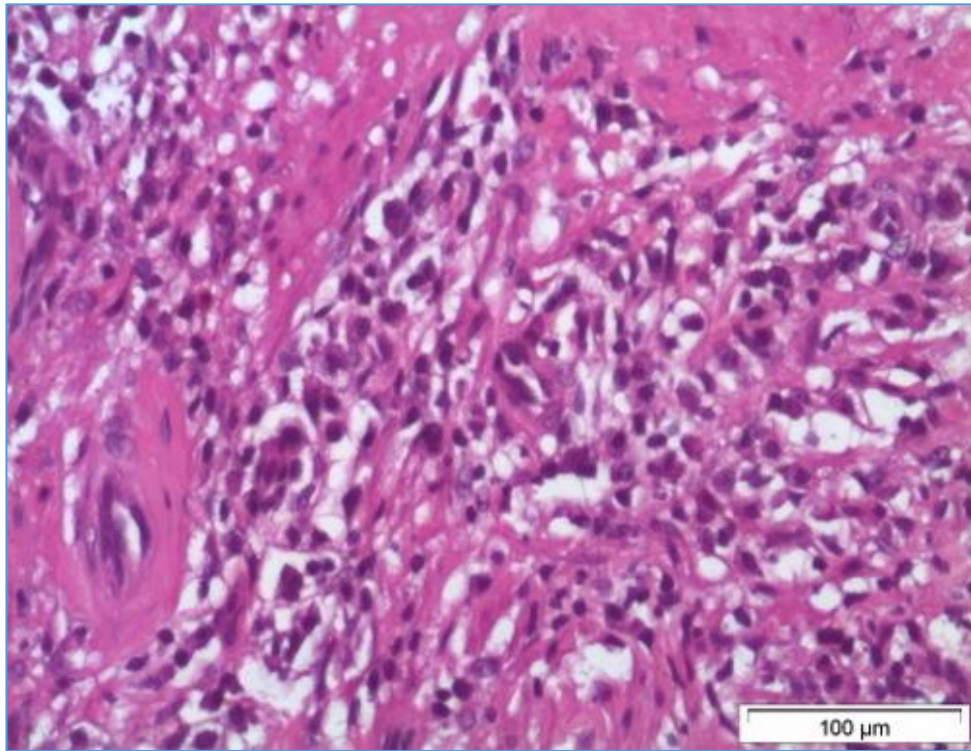


Figure 2.11. Periluminal area with severe chronic inflammation infiltrated by lymphocytes and plasma cells.

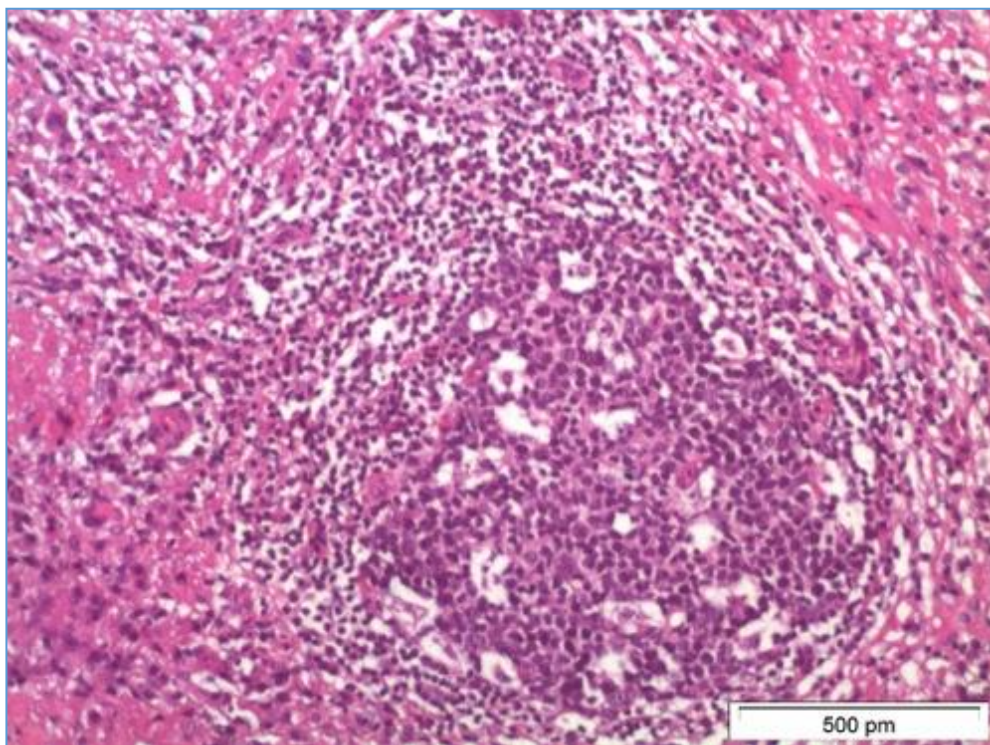


Figure 2.12. Periluminal chronic inflammation with focal lymphoid follicle formation.

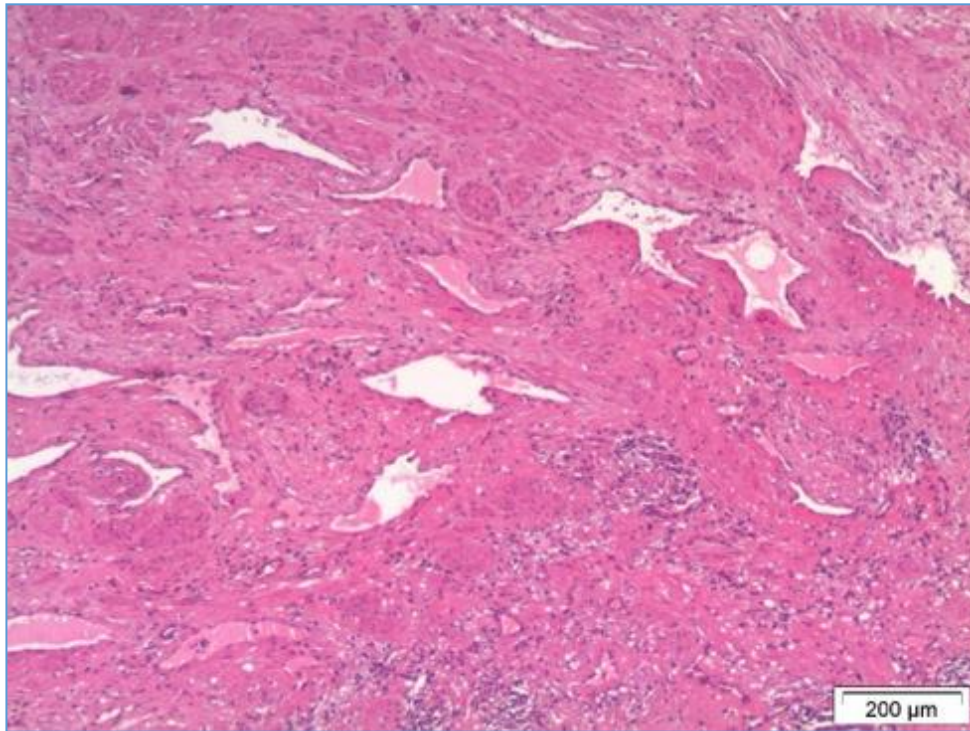


Figure 2.13. Dense fibrosis surrounds the granulation tissue in the periluminal area.

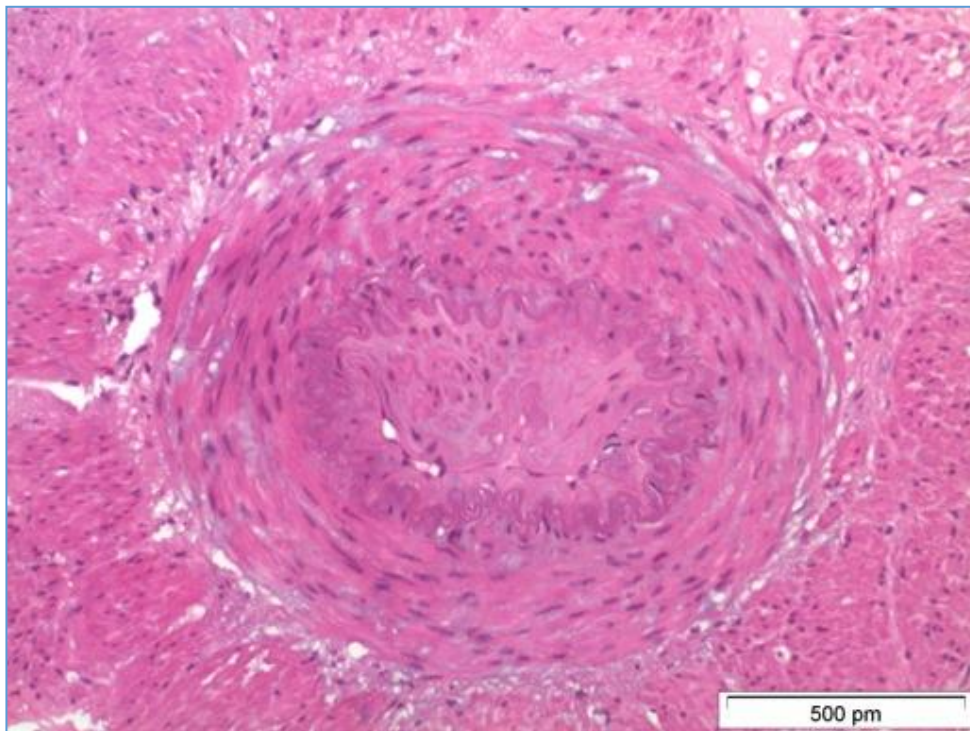


Figure 2.14. Arteries show signs of endarteritis obliterans.

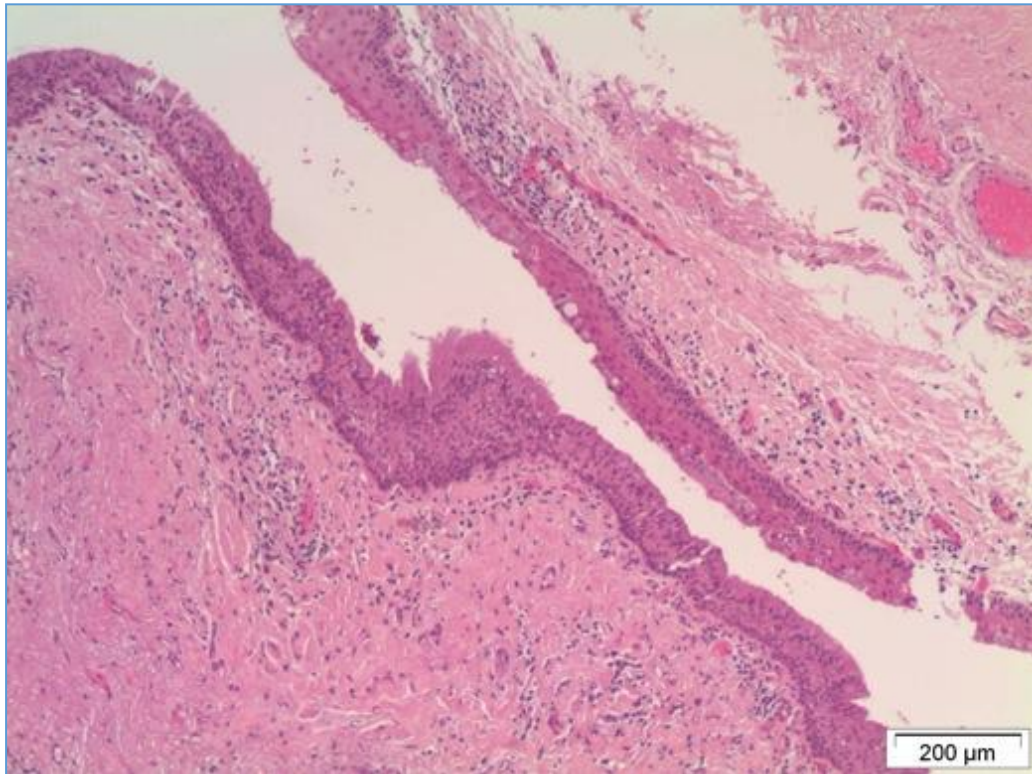


Figure 2.15. Urethral biopsy of normal appearing urethra after the stricture was excised.

2.7 Diagnosis of urethral strictures

The correct diagnosis of USD, particularly the length, the extent of the fibrosis and the location of the stricture, is important to determine the optimum treatment strategy (El-ghar *et al.*, 2010). Various investigations exist, each with its limitations.

Retrograde urethrography (RGU), which is used to diagnose urethral strictures, is the only approach that is available at the Universitas Academic Hospital (UAH). RGU is limited by technical variations in patient positioning, penile traction during imaging, (which can alter the radiographic appearance of the stricture) and the clinical interpretation of the images. Another shortcoming of RGU is its inability to demonstrate the extent of fibrosis. As a result, RGU often leads to the underestimation of the stricture length (El-ghar *et al.*, 2010).

Ultrasonography is helpful to determine stricture length and to assess the degree of spongiofibrosis. However, due to anatomical limitations, it is not recommended as the sole assessment tool for strictures. Ultrasound has advantages over RGU to determine the length of the stricture, but the RGU pinpoints the location of the stricture more

accurately. Ultrasound must be used as adjunct to the RUG for more accurate assessment (Buckley *et al.*, 2011). In a retrospective study that compared ultrasonography and RGU (Buckley *et al.*, 2011), the use of ultrasonography changed the surgical approach in 19% of patients. During this particular study the use of ultrasonography changed the surgical approach followed in forty-four (19%) patients and was integral in deciding between two equally possible approaches. The mean RGU length was 2.0 cm, whereas the mean ultrasound length was significantly longer at 3.4 cm and therefore the approach was changed from an anastomotic urethroplasty to an onlay urethroplasty (Buckley *et al.*, 2011).

Magnetic resonance imaging (MRI) urethrography offers higher diagnostic accuracy to detect urethral stricture length than conventional RGU (El-ghar *et al.*, 2010). Although MRI is more expensive than RUG and US, it can replace these modalities as a single imaging approach (Osman *et al.*, 2006). MRI has comparable results when RGU is combined with sonography. The advantage of the MRI urethrography is that it can indicate additional pathology in other regions apart from the urethra (El-ghar *et al.*, 2010). MRI compared with RGU showed that the MRI is more accurate in diagnosing the correct stricture length because it can accurately demonstrate the spongiofibrosis (Osman *et al.*, 2006). The limited number of patients used in these studies is however a shortcoming.

2.8 Controversies in the management of urethral strictures

2.8.1 Stricture length

Stricture length and location often determine the surgical technique. Length is a main contributor towards failure but the type of repair may influence the success rate (Palminteri *et al.*, 2015). In one of the largest series of 347 patients who had undergone various types of substitution urethroplasties, strictures longer than 6.5 cm were identified as a predictor of failure (Han *et al.*, 2015). Stricture lengths longer than 3.9 cm located in the bulbar urethra were identified as a potential risk factor causing failure in oral mucosa substitution urethroplasty (Palminteri *et al.*, 2015). The length of a complex urethral stricture is not yet defined, due to the regional anatomical differences in the urethra. Various stricture lengths were identified as a risk for treatment failure. Mathur *et al.* (2013) and Eswara *et al.* (2015) identified 5.0 cm and 7.0 cm as independent risk factors for

urethroplasty failures. Literature regarding lengths for specific stricture locations is lacking.

2.8.2 Stricture length and treatment approach

2.8.2.1 Stricture lengths shorter than 2 cm

Stricture lengths shorter than 2 cm located in the bulbar urethra is amendable with the anastomotic urethroplasty. When strictures are located in the penile urethra, substitution urethroplasty will be the appropriate approach.

Anastomotic urethroplasty provides good results in short bulbar urethral strictures shorter than 2 cm, where the stricture is excised and both ends of the healthy urethra is spatulated and anastomosed (Guralnick *et al.*, 2001), as illustrated in (Figures 2.16 and 2.17). Stricture length is controversial because it is uncertain which length of urethra can be excised without causing penile chordee when doing the AR. Although AR is reserved for stricture lengths shorter than 2 cm, Aghaji *et al.* (2001), report a success rate of 88% in their group of ninety-eight patients where the length was 3 cm. Eltahaway *et al.* (2007), published the largest series of 260 patients where 257 completed mean follow-up of fifty months. Their success rate was 99% for a mean stricture length of 1.9 cm (Figure 2.16).

The success rates of anastomotic urethroplasty in patients with mainly instrument related urethral strictures are summarised in Tables 2.1 and 2.2. In retrospective and prospective studies, the success rates varied between 75% and 99% at mean lengths varying from 0.6 cm to 3.8 cm. Follow-up varied between twelve to sixty-eight months.

Table 2.1. The success rates obtained in retrospective studies following anastomotic urethroplasty.

Author	Patient no.	Mean length (cm)	Follow-up (months)	Outcome % success
Aghaji <i>et al.</i>, 2001	98	3.1	12	88
Gupta <i>et al.</i>, 2007	138	2.2	26.7	83
Barbagli <i>et al.</i>, 2007	91	1 to 2	64	93
Eltahaway <i>et al.</i>, 2007	257	1.9	50.2	99
Santucci <i>et al.</i>, 2002	168	1.7	70	95
Suh <i>et al.</i>, 2013	33	1.5	42.6	88

Table 2.2: The success rates obtained in prospective studies following anastomotic urethroplasty.

Author	Patient no.	Mean length (cm)	Follow-up (months)	Outcome % success
Lumen, 2010	62	1.6	34	90
Lumen, 2012	4	0.6	31	75
Lumen, 2012	62	1.6	34	90
Morey, 2006	11	1.5	26	91
Morey, 2006	11	3.78	26	91

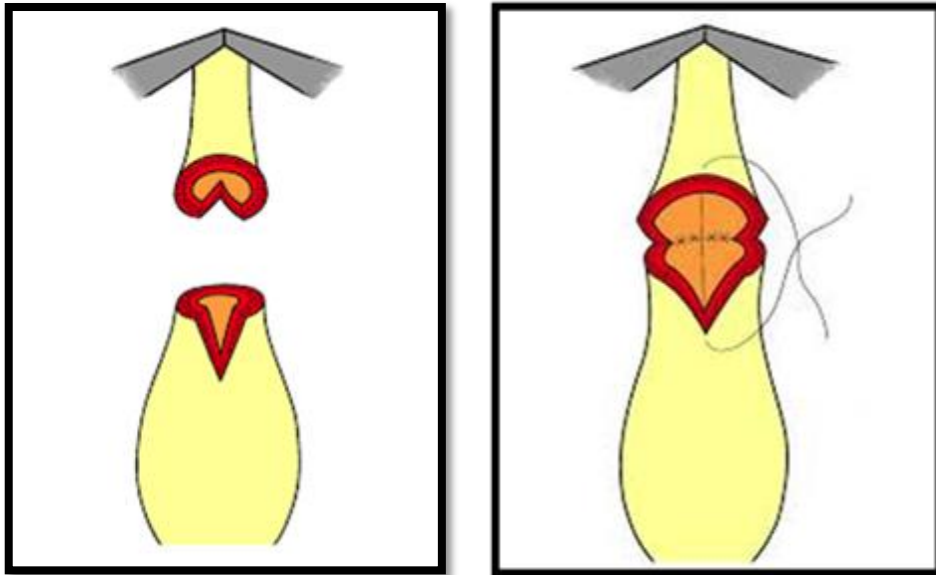


Figure 2.16. A schematic drawing of the anastomotic urethroplasty. The stricture is excised and the healthy ends are spatulated and sutured together.

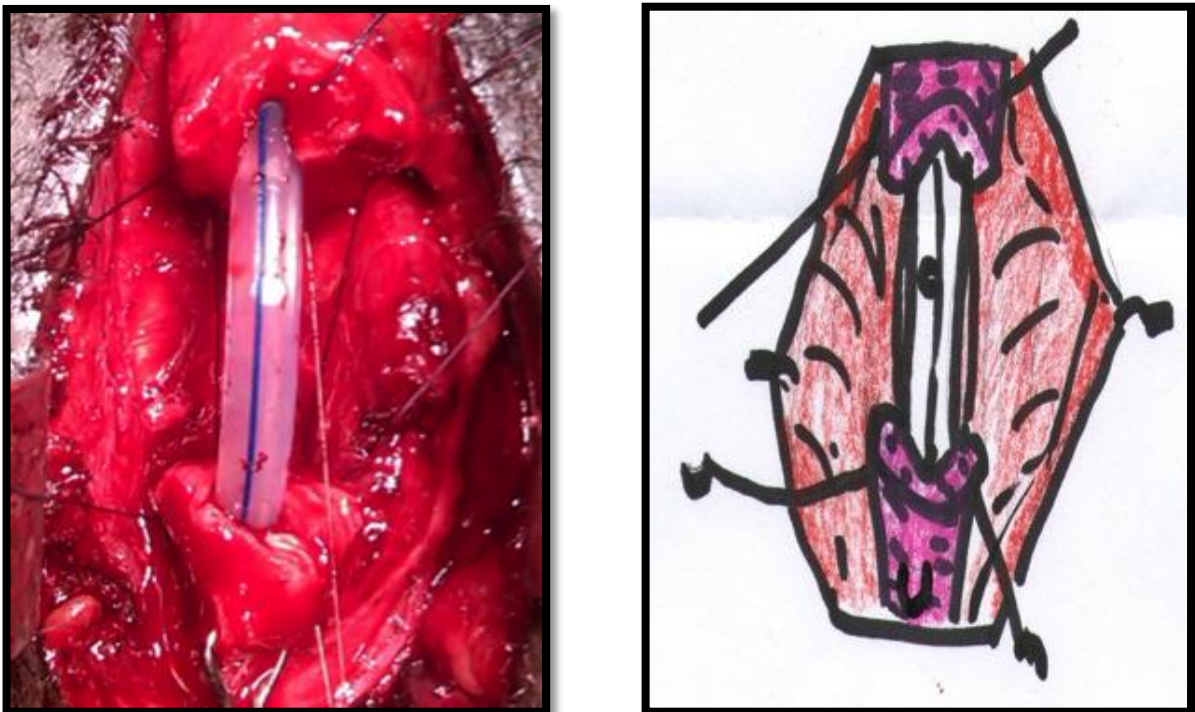


Figure 2.17 (a) The anastomosis of healthy appearing urethral ends is done with interrupted sutures over a 16 Fr catheter with interrupted sutures. (b) A schematic drawing of the anastomotic urethroplasty (u = urethra and c = catheter).

2.8.2.2 Stricture lengths between 2 cm and 4 cm

The best technique for strictures of this length has not yet been determined. The options vary between augmented anastomotic urethroplasty and dorsal or ventral buccal mucosa graft onlay urethroplasty in the bulbar urethra.

Augmented anastomotic urethroplasty combines the anastomotic urethroplasty with substitution graft for a bulbar stricture with dense fibrosis being 1 cm to 2 cm long. The segmental excision of the worst section of the stricture (but only up to 2 cm) is followed by anastomosis spatulated over a BMG placed dorsal or ventral urethral wall (Hoy *et al.*, 2013) as illustrated by (Figure 2.18a). A perineal incision is made and the urethra is circumferentially mobilised (Figure 2.18b). The narrow segment is identified and at the distal the urethra is transected at that point (Figure 2.19a). The 1 cm to 2 cm of the dense spongiofibrosis and urethra is excised (Figure 2.19b). A urethrotomy incision is made from this point through the entire extent of the stricture proximally to at least 1 cm of the healthy urethra. The proximal intrecrural space can be developed to aid in taking tension off the anastomosis, if needed. The urethra is anastomosed in the midline ventrally and dorsally sutured with 4-zero Vicral in one layer to lateral margins of the quilted BMG (Figures 2.21 and 2.22).

The success rate of AAR as a result of stricture length is summarised in Tables 2.3 and 2.4. In dorsal and ventral BMG augmented anastomotic urethroplasty, the success rates varied between 82% and 97% at mean lengths varying from 2.8 cm to 4.9 cm. Follow-up varied between fifteen to thirty-six months (Hoy *et al.*, 2013).

Table 2.3. The success rates obtained with dorsal onlay BMG augmented anastomotic urethroplasty.

Author	Study design	Patient no.	Mean length (cm)	Follow-up (months)	Outcome % success
Abdel, 2008	Retrospective	234	2.8	36	94
Abouassaly, 2007	Retrospective	58	4.2	34	82
Fransis, 2010	Prospective	30	3.2	15	94
Hoy, 2013	Prospective	163	4.9	31	97

Table 2.4. The success rates obtained with ventral onlay BMG augmented anastomotic urethroplasty.

Author	Study design	Patient no.	Mean length (cm)	Follow-up (months)	Outcome % success
Abdel, 2008	Retrospective	234	2.8	18	93
Abouassaly, 2007	Retrospective	58	4.2	34	82
Fransis, 2010	Prospective	30	3.2	15	94
Hoy, 2013	Randomised	163	4.9	31	97

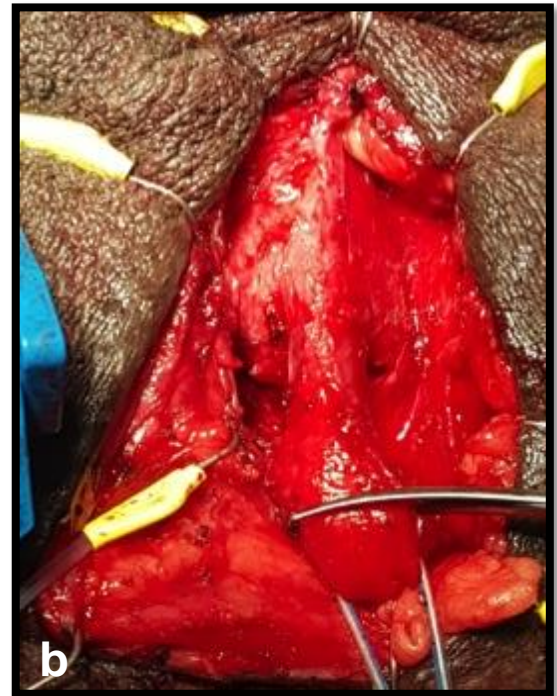


Figure 2.18. (a) The urethra is mobilised from the corpus spongiosum. (b) The urethra is mobilised and transected in the area of the urethral stricture.



Figure 2.19. (a) Approximately 1 cm of the most dense part of the stricture is excised. (b) The distal and proximal ureter is spatulated dorsally.



Figure 2.20. (a) Buccal mucosa is quilted to the corpora cavernosum. **(b)** The urethra is anastomosed ventrally with interrupted sutures.

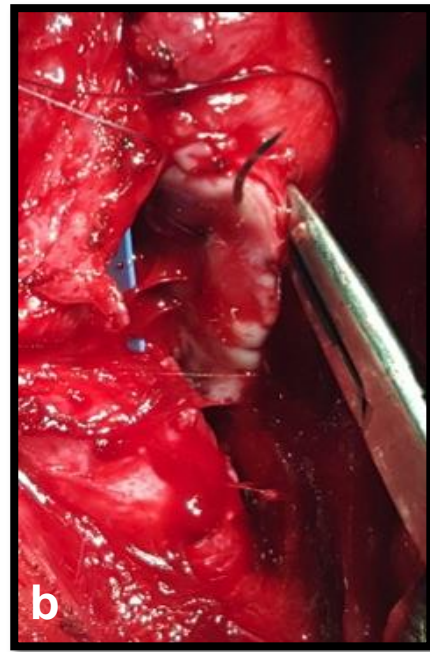
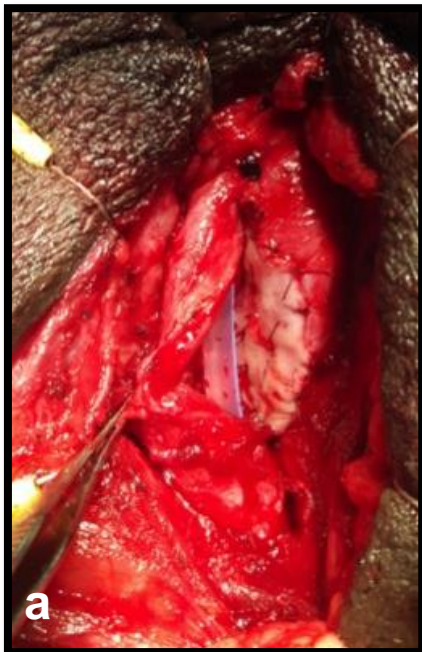


Figure 2.21. (a) A urethral catheter is passed and the dorsal part of the urethra is sutured over the catheter to the **(b)** lateral margins of the buccal mucosa.



Figure 2.22. The augmented anastomotic urethroplasty with dorsal buccal mucosa completed.

2.8.2.3 Stricture lengths longer than 4 cm

The literature agrees that strictures of this length can only be treated with substitution urethroplasty. If a bulbar stricture is longer than 4 cm, circumferential urethral reconstruction with a patch (BMG or flap) is preferred (Schwentner *et al.*, 2011). The buccal mucosa is an ideal graft because it is extremely resistant to infection (Andrich and Mundy, 2001). Buccal mucosa retains its characteristics as a free graft and the tendency to contract is about 10% compared to the 50% of free skin grafts (Andrich and Mundy, 2001). Another advantage of the use of BMG rather than genital skin, is the relatively less dissection that is required for urethroplasty, which avoids genital skin scarring.

i) Graft placement

The placement of the graft in relation to the urethra is controversial. Dorsal placement of the graft has the advantage of using the corporal bodies to provide a secure, well-vascularised graft bed, which aids to prevent the protrusion of the graft that causes

pseudodiverticulum formation. Dorsal placement of BMG is currently preferred when BMG urethroplasty is done (Peterson *et al.*, 2004). Ventral location provides the advantages of ease of exposure and good vascular supply by avoiding circumferential rotation of the urethra. Ventral urethrotomy allows the lumen to be clearly delineated, thus enabling the surgeon to identify mucosal edges, measure the size of the plate, do a watertight anastomosis and, if necessary, excise a portion of the stricture and do dorsal re-anastomosis (Wessells, 2002). Three variations for BMG placement - ventral, dorsal and lateral - had similar success rates of 83%, 85% and 71% respectively. It must be noted that the patient numbers from which this conclusion was made, were small (Barbagli *et al.*, 2005). The five-year success rate of dorsal (95%) and ventral onlay (86%) urethroplasty with BMG was similar (Andrich *et al.*, 2001). Although the re-stricture rates were similar in a series of 109 patients by Dubey *et al.* (2003), the ventral placement of the grafts had a higher number of complications compared to the dorsal onlay procedures. Significant complications of the ventral versus dorsal placement of the graft was post-void dribbling (39% vs. 23%), ejaculatory dysfunction (20% vs. 5%) and pseudo-diverticulum (26% vs. 3%). The re-stricture rate was the same for dorsal and ventral onlay procedures (Dubey *et al.*, 2003).

The *dorsal onlay BMG urethroplasty* was developed between 1995 and 1996 by Barbagli *et al.* (1995). The bulbar urethra is completely mobilised from the corpora cavernosa and rotated 180°. The stricture is opened along the dorsal surface. The skin or buccal mucosal graft is spread and sutured to the adjacent corpora cavernosa (Figure 2.23). The right and left mucosal margin of the urethra is sutured to the graft edge. The rationale behind this technique is that the corporeal body remains a healthy host to receive the free graft. Another advantage is spread fixation of the graft onto a fixed surface of the corpora, which may prevent potential graft shrinkage (Barbagli *et al.*, 2004).

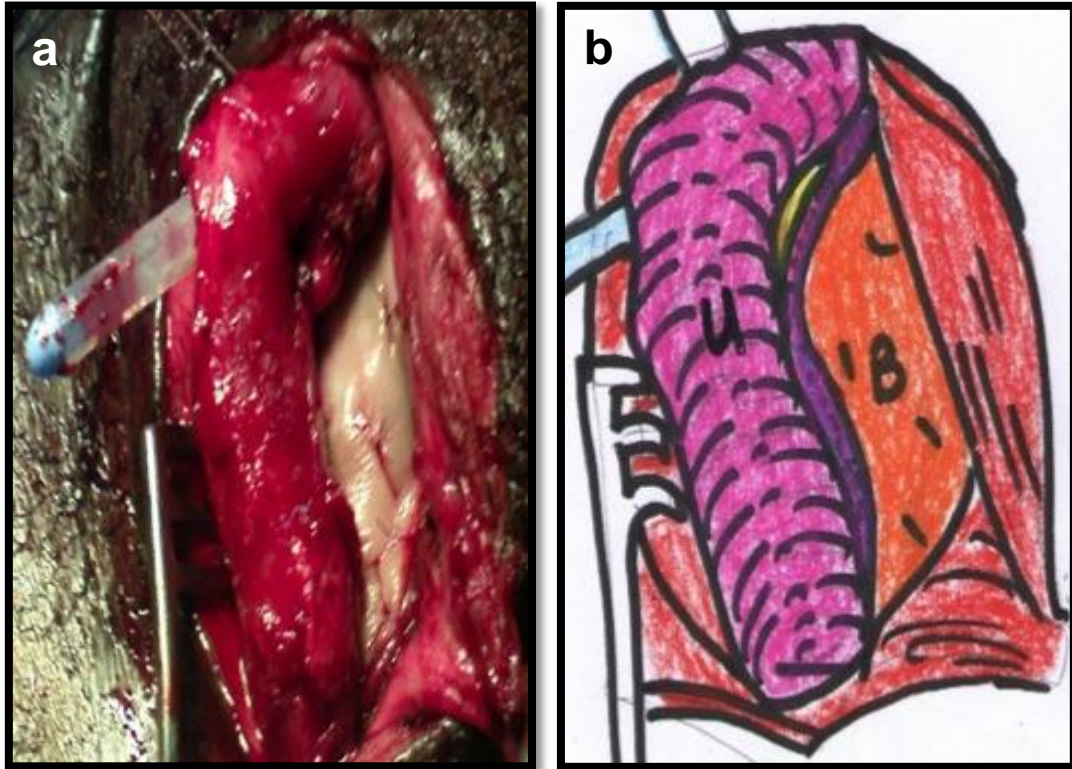


Figure 2.23. The dorsal BMG onlay urethroplasty: **(a)** The urethra is mobilised from the corpora cavernosum and the urethra is opened in the dorsum over the stricture area. The BMG is quilted to the corpora cavernosum and the urethra is closed over the BMG. **(b)** A schematic drawing of the dissection (U = urethroplasty and B = buccal mucosa graft).

The success rates of the dorsal and ventral BMG onlay urethroplasty as a result of stricture length are summarised in Tables 2.5 and 2.6. The success rate of the dorsal BMG varied between 75% and 97% at mean lengths varying between 3.5 cm and 5.6 cm. It is important to note that the urethral stricture lengths were not recorded in ten studies. Follow-up varied between 16 to 120 months.

Table 2.5. The success rates obtained with the dorsal onlay BMG graft urethroplasty.

Author	Study design	Patient no.	Mean length (cm)	Follow-up	Outcome % success
Aldaquad, 2014	Randomised	25	4.9	23	88
Andrich, 2001	Retrospective	42	3.2	60	95
Barbagli, 2008	Retrospective	22		41	77
Barbagli, 2005	Retrospective	27	NA	42	85
Dubey, 2005	Retrospective	75	5.6	36	90
Dubey, 2007	Randomised	27	5.6	23	89
Mathur, 2011	Retrospective	24	7.1	16	92
Pansadoro, 2003	Retrospective	56	4.3	41	97
Raber, 2005	Prospective	13	3.5	51	80

Ventral buccal mucosa onlay urethroplasty. The urethra is approached through a perineum incision. The bulbospongiosus muscle is split. The stricture is identified and opened through a ventral slit in the urethra (Figure 2.24). The BMG or skin graft is splayed over the stricture area (Figure 2.25). The BMG is sutured to the urethral mucosa with a 4-zero Vicral after passage of a 16 Fr catheter (Figure 2.26). The urethra spongiosum is closed over the BMG and the urethroplasty is completed (Figure 2.27).

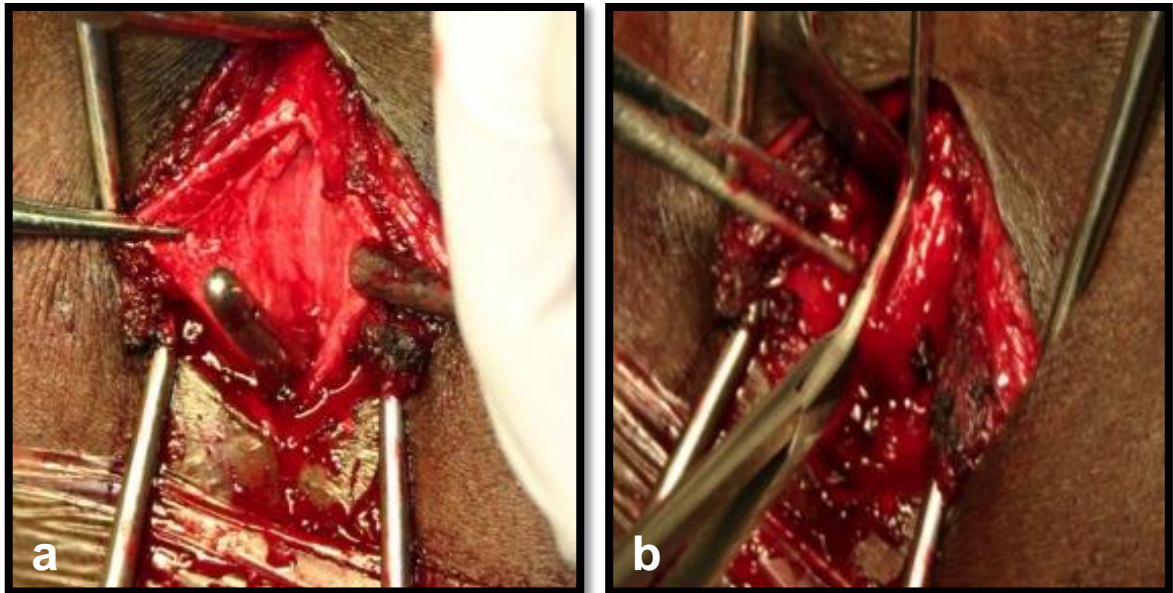


Figure 2.24. The urethra is approached through a perineum incision. **(a)** The stricture is identified. **(b)** A stricturotomy is done with a ventral longitudinal incision.

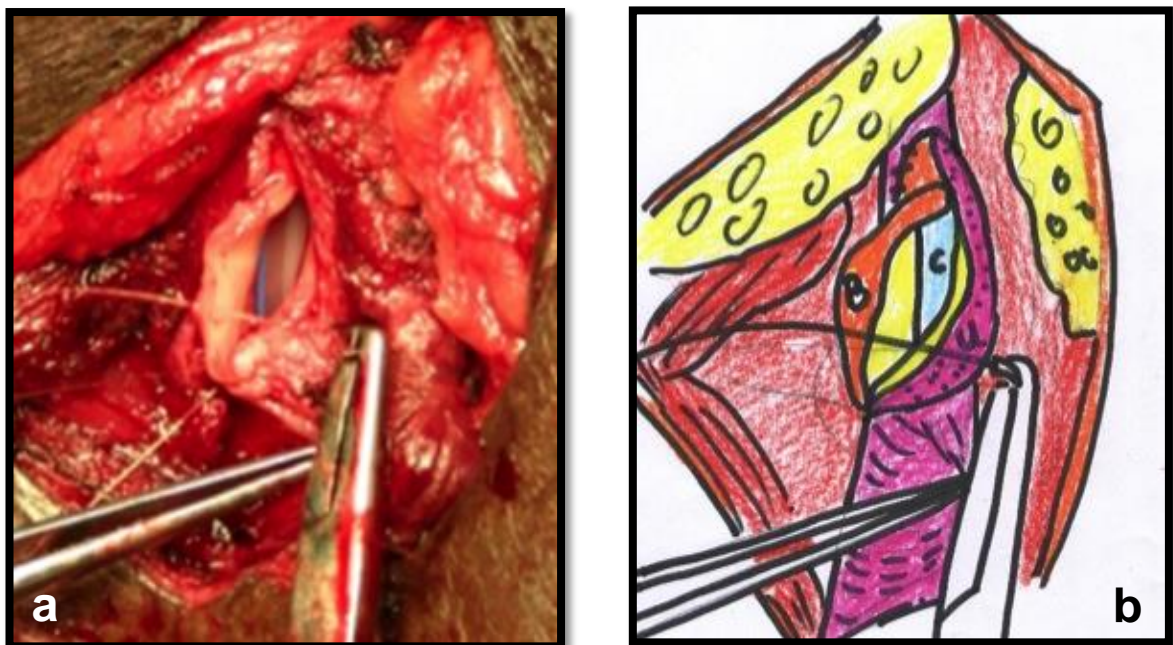


Figure 2.25. The ventral BMG onlay urethroplasty: **(a)** The corpora spongiosum is opened over the stricture area. The urethra is closed over the stricture area with a BMG. **(b)** Schematic drawing of the dissection (U = urethroplasty, C = catheter and B = buccal mucosa).

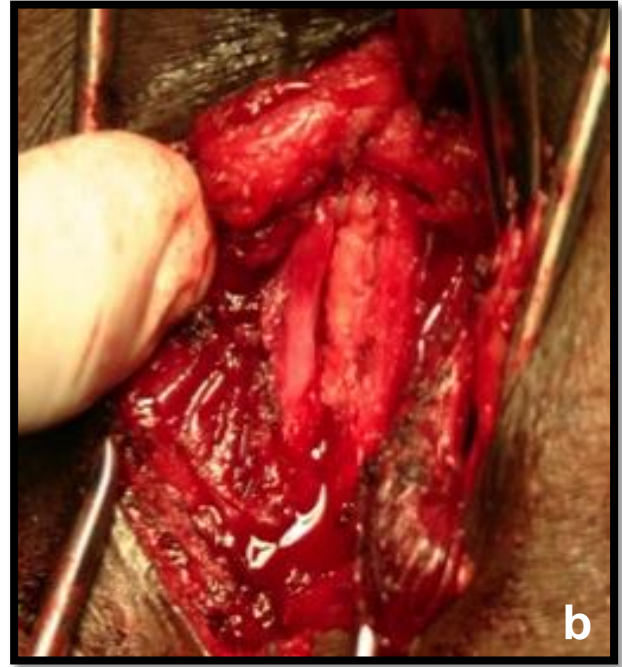
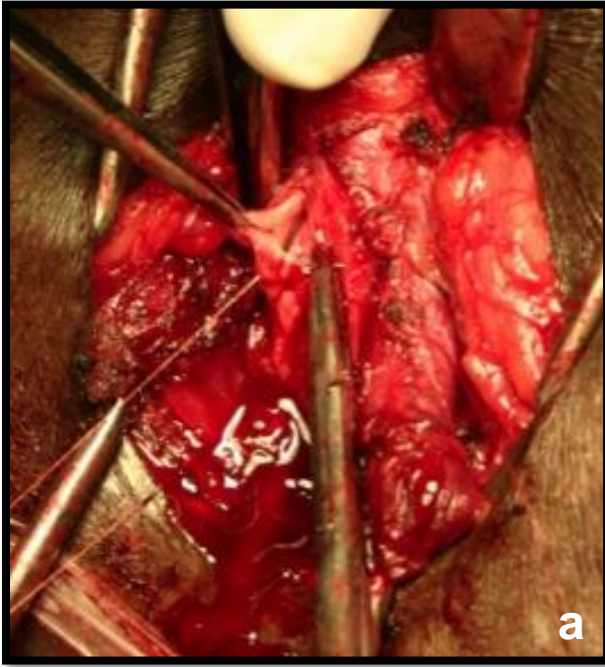


Figure 2.26. (a) The BMG is sutured to the urethra over the stricture area. **(b)** The BMG sutured over the stricture.

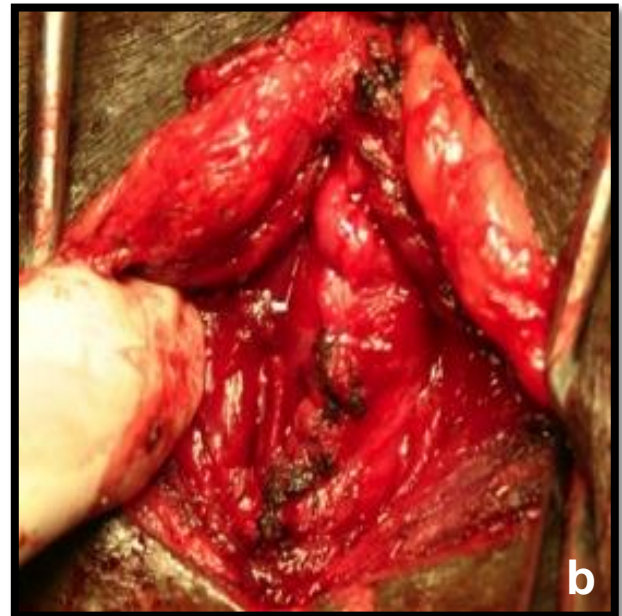
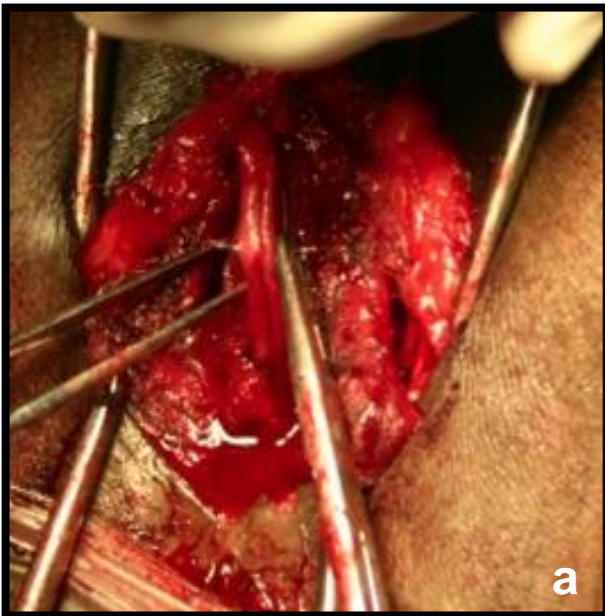


Figure 2.27. (a) The corpus spongiosum of the urethra is closed over the BMG. **(b)** The final appearance of the buccal mucosa graft.

Table 2.6. The success rates obtained with the ventral onlay graft urethroplasty.

Author	Study design	Patient no.	Mean length (cm)	Follow-up	Outcome % success
Andrich, 2001	Retrospective	29	NA	60	86
Barbagli, 2008	Retrospective	93	NA	36	91
Barbagli, 2013	Retrospective	214	4.36	54	86
Mellon, 2014	Retrospective	144	3.14	42	75
Dubey, 2003	Retrospective	18	4.22	46	78
Elliott, 2003*	Retrospective	42	5.3	47	90
Fichter, 2004	Retrospective	32	4.3	83	75
Heinke, 2003	Prospective	38	5.6	23	80
Heinke, 2010	Prospective	38	5.2	23	80
Kane, 2002	Retrospective	53	3.64	25	94
Mellon, 2014	Retrospective	99	3.14	120	77
Raber, 2005	Retrospective	13	3.5	41	85

ii) Flap versus graft

There is no conformity with regard to the advantage of using skin flaps rather than grafts that include buccal mucosa and penile skin free grafts. A controversial issue is the use of buccal mucosa graft (BMG) or penile skin flap for substitution urethroplasty for long segment urethral strictures, although no difference in outcomes of the two approaches was reported (Whitson *et al.*, 2008; Dubey *et al.*, 2003). Panurethral strictures involve the entire length of the urethra including the penile and bulbar regions (Waxman SW *et al.*, 2006). Pedicled penile skin flap urethroplasty is often used to repair complex urethral strictures with lengths of up to 15 cm (Waxman *et al.*, 2006). The rationale behind the use of vascularised pedicle skin flaps as a urethral substitute is the fact that the flap carries its own blood supply and it is supposedly an improvement on the free graft substitute. The main disadvantage is the ballooning of the flap at the urethroplasty site, which leads to irritative lower urinary tract symptoms and post-void dribbling (Schwentner *et al.*, 2011). Another disadvantage of the vascularised pedicle skin flaps as a urethral

substitute is the more extensive dissection that is needed to complete the urethroplasty (Dubey *et al.*, 2007). The success rate of the circular island skin onlay flap is reported as being 90% (Schwentner *et al.*, 2011). The penile skin flap urethroplasty for complex anterior urethral strictures have good short and long-term success rates of 95%, 89%, 84% and 79% at one, three, five and ten years respectively (Whitson *et al.*, 2008). Hussein *et al.* (2011) reported similar results in a prospective randomised study for instrument and idiopathic related strictures, where penile circular skin graft was compared with penile skin pedicled flap when substitution urethroplasty was done for strictures with a mean length of 15.2 cm. Their re-stricture rate was 28% in patients who had had the penile circular skin graft urethroplasty and 21% in patients who had had the penile skin pedicled flap urethroplasty (Hussein *et al.*, 2011). The disadvantage of the penile skin flap compared to the BMG is that the procedure is technically more complex, associated with higher morbidity and less preferred by patients (Dubey *et al.*, 2007). In a randomised controlled trial on intermediate follow-up, BMG urethroplasty had a success rate of 90%, similar to the success rate of 86% of penile skin flap urethroplasty (Dubey *et al.*, 2007). Barbagli *et al.* (2008) reported a lower success rate of 66% compared to the 79% by Hussen *et al.* (2011) in a retrospective analysis for catheter and trauma related urethral strictures when genital skin grafts were used for onlay bulbar urethroplasty. It appears from the literature that the success rates for pedicled penile skin urethroplasty varies between 60% and 89% (Table 2.7).

The success rates of the dorsal pedicled island penile skin urethroplasty as a result of stricture length is summarised in Table 2.7.

Table 2.7 The success rates obtained with dorsal pedicled island penile skin flap urethroplasty.

Author	Study design	Patient no.	Mean length (cm)	Follow-up	Outcome % success
Bhandari, 2001	Randomised	19	4.95	28	89
Dubey, 2003	Retrospective	23	6.56	22	83
Lumen, 2010	Prospective	5	7.1	32	60
Mathur, 2014	Retrospective	58	6.2	44	81
Raber, 2005	Prospective	17	3.5	51	76
Srivastava, 2012	Retrospective	40	7	42	85
Srivastava, 2012	Retrospective	60	8.9	46	87

2.9 Urethral stricture location

Stein *et al.* (2013) reports in their large retrospective study of 1877 patients that strictures located in the bulbar area (1046 or 56%), are more common than penile urethral strictures (506 or 27%). The incidence of penile urethral strictures is increasing due to the use of instrumentation and lichen sclerosis (LS) (Venn *et al.*, 1998). Stricture location has an effect on stricture length where penile strictures tend to have longer mean stricture lengths compared to that of bulbar strictures; mean of 6.1 cm vs. 3.1 cm (Fenton *et al.*, 2005).

2.10 Single-stage versus two-stage repair for long strictures

Penile urethral surgery tends to be more complex than bulbar strictures due to the thin spongiosum and narrow urethral lumen with higher numbers of less satisfactory outcomes (Andrich *et al.*, 2008). Penile urethroplasty can be a one- or two-stage procedure. A one-stage reconstruction involves the creation of a tube neourethra from free graft or skin flap at the time of surgery. (Palminteri *et al.*, 2002). A two-stage reconstruction involves the creation of a flat neourethral plate from free graft or skin flap at the time of the surgery and the urethral reconstruction is completed three to six months later. Andrich *et al.* (1999) reported that the re-stricture rate was lower after a two-stage procedure (25%) than the one-stage procedure (38%). The revision rate of the two-stage procedure in the

penile urethra was as high as 50% (Andrich *et al.*, 2003). One-stage circumferential penile skin flaps have lower success rates when compared to two-stage repairs using free grafts, although Wintson *et al.* (2008) reported that success rates of circular fasciocutaneous flaps for single stage reconstruction has reached 79% after ten-years follow-up. Two-stage repairs are generally accepted in patients with inflammatory urethral strictures secondary to lichen sclerosis (Kulkarni *et al.*, 2009). Another indication for a two-stage urethroplasty is those patients who had previously undergone urethroplasty with significant scarring of the surrounding skin, although the revision rate in these patients was 20%. The two-stage Johanson procedure, with or without free graft, is the conventional technique to repair anterior pan-urethral strictures. Hair-growing scrotal and perineal skin can result in chronic urinary tract infections, lithogenesis, fistulation, and diverticulum formation of the reconstructed urethra. These are drawbacks of this approach, which led to a modification of the Johanson technique (Lapides, 1959).

A modification of the Johanson two-stage technique is illustrated in (Figure 2.28). The fasciocutaneous flap was created and used instead of scrotal skin to create the neourethra during the second stage. This will avoid hair growth in the neo-urethra (Figures 2.28 to 2.31).

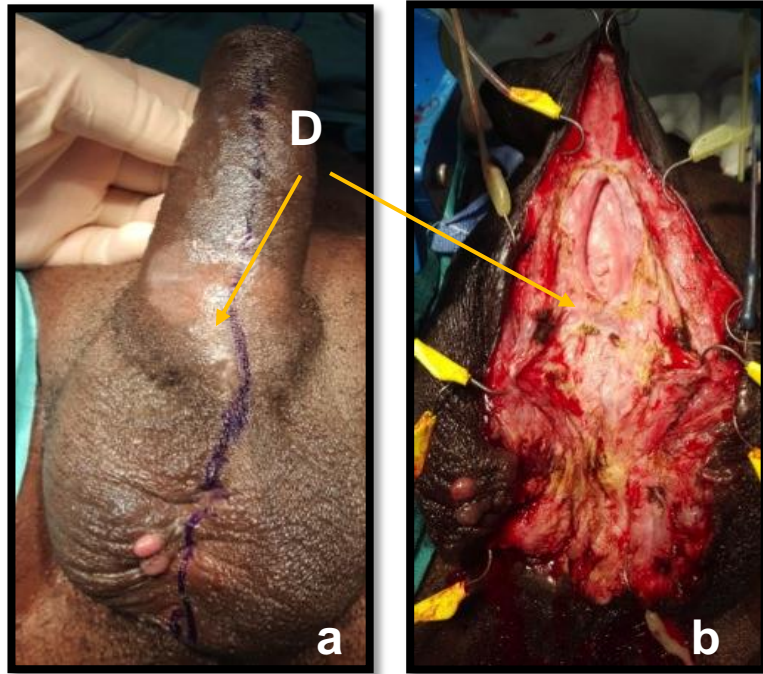


Figure 2.28. A patient with panurethral stricture disease with visible perineum skin lesions and fistula (a). Severe fibrosis visible and diverticulum (b) in the area of the penile-bulbar urethra. (D) shows the diverticulum.

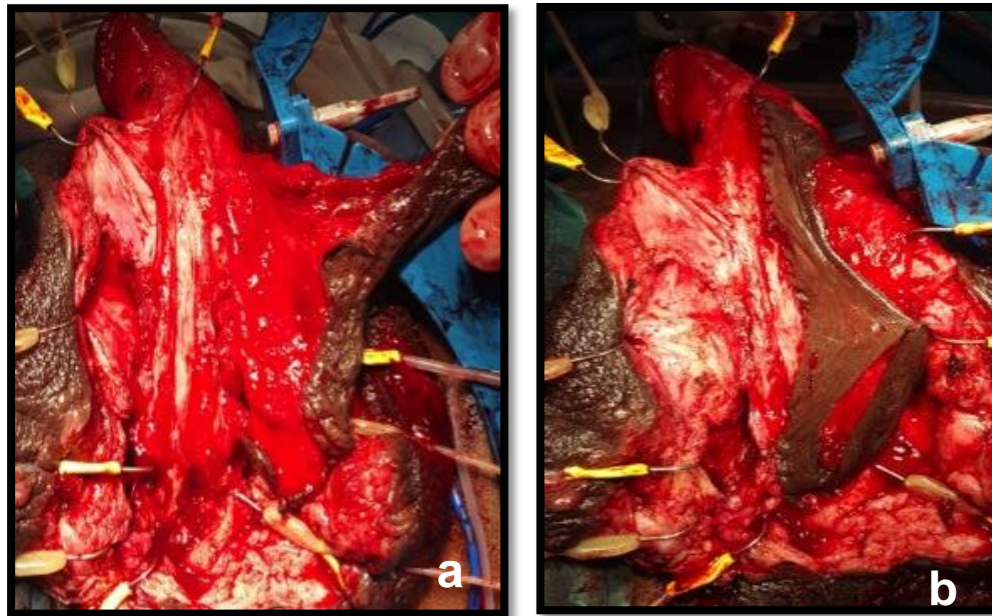


Figure 2.29 A Fasciocutaneous penile skin flap is created and sutured to the splayed urethra (a) and sutured to the left margin of the splayed urethra (b).

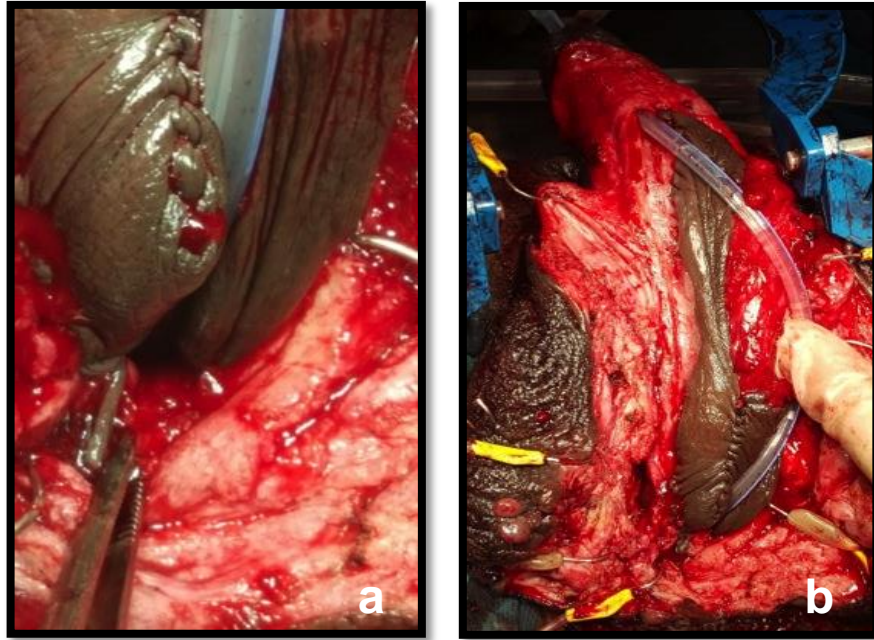


Figure 2.30. (a) The proximal bulbar urethra is completely fibrotic and (b) the fasciocutaneous penile skin flap is sutured to the proximal urethra.

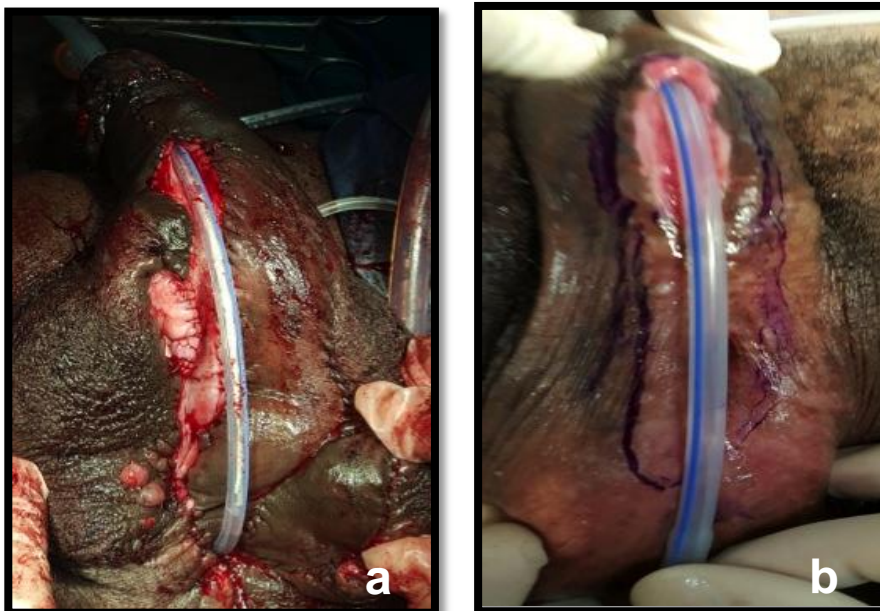


Figure 2.31. Post-surgery of the first stage of a two-stage urethroplasty The appearance of the (a) first stage six months later before closing the urethra with skin from the lateral margins of the urethra indicated by the purple lines (b).

2.11 Obliterative urethral lumens

There is no gold standard for the treatment of long bulbar or penile strictures that are more or less obliterative. There is no distinction between urethroplasty success rates where the urethral lumen is more or less completely obliterated and where the lumen is significantly narrowed but not closed. One of the few prospective studies showed that the percentage urethral narrowing of 74% was associated with failure of direct vision urethrotomy (DVIU) (Mandhani *et al.*, 2005). An obliterative urethral lumen does not influence the complexity of the urethral stricture and was excluded from the urethral stricture score (U-score) validation (Eswara *et al.*, 2015). Anastomotic urethroplasty (AR) is an excellent approach when dealing with obliterative lumens where the obliterative segment can be completely excised but not suitable for all strictures lengths and locations (Eltahawy *et al.*, 2007). On the other hand, standard patch urethroplasties with free grafts or pedicled penile skin may be more appropriate (Barbagli *et al.*, 2003). If the whole stricture is more or less obliterative, the alternatives are long pedicled penile skin repair as a one-stage approach (Carney *et al.*, 2002).

2.12 Urethral stricture repair deterioration

Stricture recurrence may occur as much as fifteen years after urethroplasty. Therefore, a long term follow-up is recommended in order to determine the treatment outcome and patients should be informed accordingly. The type of approach may affect the long-term deterioration of the repair. Anastomotic urethroplasty had a re-stricture rate of 14%, significantly lower than the 58% for substitution urethroplasty at a fifteen-year follow-up. (Andrich *et al.*, 2003). The type of substitution used for urethroplasty has an effect on stricture deterioration. This is illustrated by Barbagli *et al.* (2014) where oral mucosa grafts had a slower re-stricture rate compared to that of penile skin grafts. Their stricture free rates were 80% and 69% respectively (Barbagli *et al.*, 2014).

2.13 Definition of treatment failure

There are no defined protocols for follow-up assessment of failure. At UAHC history taking is employed as the only follow-up approach. In general, when a patient has difficulty to void it is regarded as a failure. There are various approaches to identify stricture recurrence (Table 2.8).

History taking is the only modality where failure is defined as the development of obstructive lower urinary tracts symptoms, which lead to further investigation for stricture recurrence. (Andrich *et al.*, 2001, Pansadoro *et al.*, 2003).

Uroflowmetry is a non-invasive investigation, which evaluates voiding function in patients experiencing lower urinary tract infection. It involves measuring of the maximum voiding rate of a patient (Q-max). The Q-max rate alone may not be sensitive enough to replace cystoscopy when screening for stricture recurrence in all patients, especially in younger men where baseline flow rates are higher. In older men of forty years and older benign prostatic hyperplasia may influence a lower Q-max. When a Q-max of < 10mL/s is used as the cut-off point, the sensitivity is 39% to 47% to predict bladder outlet obstruction. A Q-max of < 15 ml/s is defined as a failure by various authors but the difficulty lies in the fact that a decrease in Q-max occurs only when the urethral diameter is less than 10F (Sing *et al.*, 2009).

Any instrumentation, dilatation and/or catheterisation necessary after treatment is regarded as treatment failure (Kulkarni *et al.*, 2009).

Radiographic evidence of stricture recurrence on RGU is defined as failure. RGU and endoscopy are the two approaches that are the most objective. (Asopa *et al.*, 2001). Imaging options are retrograde urethrogram (RGU), voiding cystourethrogram (VCUG), and pericatheter RGU.

Table 2.8: The definition of treatment failures and the follow-up methods are summarised in the table.

Author	Type of graft	Definition of failure	Follow-up method
Dubey <i>et al.</i> , 2003	BMG	Need for urethral dilatation/with or without DVIU.	<ul style="list-style-type: none"> • Uroflowmetry 6-monthly. • Urethrography 6, 12, 18 months.
Eliot <i>et al.</i> , 2003	BMG	Symptoms of recurrence or change in urinary stream.	<ul style="list-style-type: none"> • Urography 3 weeks, then 3, 6, 12 months and then annually.
Kane <i>et al.</i> , 2002	BMG	Recurrence on that urethrography needs intervention.	<ul style="list-style-type: none"> • Uroflowmetry 3, 6, 12 months, then annually. • Symptom score and urethrography 3 weeks and at 3 months.
Mathur <i>et al.</i> , 2010	TA	Uroflowmetry Q-max < 20 ml/s Requiring urethral dilatation.	<ul style="list-style-type: none"> • Uroflowmetry and patient satisfaction 6,12, 24 and at 36 months. • Urethrography 6, 12, 24 and 36 months.
Pansodoro <i>et al.</i> , 2003	BMGU	Recurrence of symptoms.	<ul style="list-style-type: none"> • Uroflowmetry. • Urethrography 2 weeks, 3, 6 and 12 months.
Barbagli <i>et al.</i> , 2004	PS	Any instrumentation.	<ul style="list-style-type: none"> • Uroflowmetry 3, 6, and 12 months. • Urethrography 3 weekly, then as required.
Schwentner <i>et al.</i> , 2010	PS and GS	Presence of symptoms and low flow rate.	<ul style="list-style-type: none"> • Uroflowmetry/PVR 3, 6, 9, and 12 months. • Urethrography at catheter removal, then if required.

BMG = buccal mucosa graft; TA = tunica albuginea urethroplasty; PS = penile skin urethroplasty; GS = groin skin graft.

2.14 Definition of successful treatment outcome

Success can be defined in either functional or anatomical terms. Functional success is assigned if the patient-reported outcome measures reveal improvement in voiding symptoms and urinary quality of life. Functional success is determined with non-invasive testing such as questionnaires and uroflowmetry. Anatomical success is assigned when doing a flexible scope after urethroplasty, which can traverse the reconstructed urethra without difficulty. An optimal follow-up strategy will have to determine functional outcomes and prevent invasive testing (Erikson *et al.*, 2017).

2.15 Research aim and objectives

2.15.1 Aim

The primary aim of this research was to determine a treatment protocol for infective urethral stricture disease, which can be implemented at hospitals in Central South Africa. This will be achieved through four secondary objectives.

2.15.2 Objectives

- To conduct a retrospective study to determine the long-term outcome of treatment procedures by creating a database for patients with a minimum follow up of seven years who had been treated at Universitas Academic Hospital Complex from 2005 until 2009.
- To determine whether the double layer continuous running suture anastomosis after excision of the stricture will improve anastomotic urethroplasty outcome for bulbar urethral strictures.
- To determine the success of incorporating the fibrotic urethra as part of a two-stage repair combining dorsal BMG onlay with pedicled penile skin.
- To determine the role of stricture length, location and obliterative lumens in the treatment outcome of infective urethral strictures.

2.16 Research plan

2.16.1 Literature study

A literature search was done on the Medline database using the search terms ‘urethral stricture, urethral stricture disease, urethroplasty, buccal mucosa and penile skin’ from 2000 to 2013. Original English articles that were available were included. The criteria for exclusion were posterior urethral repair, previous hypospadias repair and review articles. It was decided to include original articles published in peer reviewed journals regarding the outcome of different urethroplasty techniques. Articles presenting opinions rather than evidence were excluded. The abstracts of 115 original research articles on the repair of anterior urethra strictures were included. The surgical techniques in the literature were challenging to compare, mainly because they lack information about stricture location and lengths. The selection of surgical techniques is often biased and most of the time governed by the surgeon’s preference and expertise.

2.16.2 Creation of a database

An electronic database for patients treated for urethral strictures from 2005 until 2009 was created. For this purpose, data of patients who were treated for urethral stricture disease as per the clinic's written notes as well as the hospital's Meditech electronic system were collected. The radiological files and the retrograde urethrograms were studied and lengths and location of strictures documented. The Meditech hospital system was used to trace each patient's clinic as well as casualty visits post-treatment to determine the time in months to the adverse event. When patients had an adverse event and visited any other training hospital, the information was also available on the Meditech hospital system at Universitas hospital. Patients with incomplete patient files and patients that were followed up for periods less than five years were excluded from the database. Through the implementation of these guidelines 401 patients with complete records could be included in this research. This has been provided in appendice A: Data form, appendice B: Statistical figures used for data interpretation and appendice C: A primary component analysis of all procedures.

Chapter 3

ARTICLE 1

The long-term outcome of surgically treated anterior urethral stricture disease in central South Africa: A 7-year follow-up

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Abstract

Objective: To report the long-term outcomes of surgical treatment of anterior urethral strictures in central South Africa.

Methods: The hospital records of 308 patients treated for anterior urethral stricture disease between January 2005 and December 2008 were reviewed. Outcomes were analysed firstly according to age, presenting symptoms, aetiology, location and length of the stricture. Thereafter, the long-term outcomes were analysed according to surgical procedure. Finally, outcomes of surgical procedure were further sub-analysed according to type of obstruction, aetiology, length and position. Treatment failure was defined as symptomatic urinary obstruction requiring any urethral intervention.

Results: The mean stricture length was 2.1 cm (range 0.2 cm to 10 cm). The aetiology was gonococcal urethritis (81%), trauma (8%), catheter-related (6%) and unknown (5%). The overall treatment success rate for infective strictures was 43% versus 72% for traumatic strictures ($p=0.019$; Hazard ratio (HR) 2.6; 95% confidence interval (CI) 1.225 – 5.597). Stricture lengths longer than 3 cm presented with a 30% lower success rate than the other length groups, 56% (0.1 to 0.9 cm), 45% (1.0 cm to 1.9 cm) and 53% (2.0 cm to 2.9cm) ($p=0.008$). The success rates at 7-year follow-up for direct vision internal urethrotomy (DVIU) alone was 17% and for DVIU with follow-up dilations 43%. The success rate for the various types of urethroplasty was as follows - anastomotic urethroplasty (58%), augmented anastomotic urethroplasty (80%), dorsal and ventral buccal mucosa graft (BMG) on-lay urethroplasty (65% and 27% respectively) and circular pedicled penile skin flap urethroplasty (cPFU) (13%). The dorsal BMG on-lay had a higher success rate (65%), compared to the success rate of 27% in the 11 patients who had had ventral on-lay BMG urethroplasty ($p=0.044$).

Conclusions: In these series, treatment failure was higher for infective urethral strictures when compared to traumatic strictures. Stricture length longer than 3 cm is a risk for treatment failure. Dorsal placement of the BMG is preferable when substitution urethroplasty is done for extensive infective urethral strictures.

Key words: Urethral stricture, urethroplasty, buccal mucosa graft, inflammatory.

Introduction

Endoscopic and urethroplasty procedures are commonly used to treat anterior urethral disease. Stricture location, length, aetiology, co-morbidities and the surgeon's capabilities all play a role in the selection of treatment procedures (Roehrborn *et al.*, 1994). For example, inflammatory urethral strictures tend to be longer in length and tend to recur because of extensive underlying fibrosis, hence complex urethral strictures with

obliterated lumens are repaired preferably using circular fasciocutaneous penile skin flaps.³ In the developing world infectious aetiology is the most important cause of urethral obstruction, causing obstruction of various lengths in different locations in the urethra. Success rates after urethroplasty for urethral stricture disease are often cited as exceeding 90%.⁴ In order to develop a rational surgical approach to urethral obstruction that is specific to populations in the developing world with a high incidence of inflammatory urethral obstruction, careful analyses of retrospective data are imperative. This should not only include age and mode of presentation, but also aetiology, length and location of the obstruction. The long-term outcomes of different surgical interventions can then be further analysed in relation to the underlying pathology. Thus, the failure rates of each procedure can be evaluated in a specific setting of aetiology, position and length of obstruction as well as the procedure itself. It is important to evaluate the primary pathological process causing the urethral stricture and the impact on outcomes of surgical treatment.

The aim of this study is therefore to critically evaluate the long-term results of patients treated for anterior urethral stricture disease with direct vision internal urethrotomy (DVIU) and various urethroplasty techniques at a single institution in central South Africa.

Methodology

A retrospective analytical cohort study was performed using the files of 308 patients who underwent treatment for anterior urethral disease and had had a minimum follow-up of seven years after the first procedure. Outcomes were analysed firstly, according to age, presenting symptoms, aetiology, location and length of the stricture. Thereafter, the long-term outcomes were analysed according to surgical procedure. Finally, outcomes of surgical procedures were further sub-analysed according to type of obstruction, aetiology, length and position.

The procedures included DVIU, DVIU followed by urethral dilatations three-monthly for two years (DVIU & DIL), anastomotic urethroplasty (AR), augmented anastomotic repair (AAR), dorsal BMG on-lay urethroplasty (DBMGU), ventral on-lay BMG urethroplasty (VBMGU) and one-stage circular pedicled penile skin flap urethroplasty (cPFU). The success rates of patients who received DVIU followed by three-monthly urethral

dilatations in the clinic for two years were determined after the last dilatation. Patients with failed hypospadias repairs and membranous urethral strictures were excluded. All patients underwent a pre-operative retrograde urethrography (RGU) and prograde urethrograms to determine the length and position of the urethral stricture. Unfortunately, ultrasonography was not available as an adjunctive investigation, which would have been more accurate in determining the extent of fibrosis.⁴ Four stricture positions were documented: Penile, penobulbar, bulbar and panurethral stricture disease. The penobulbar location included strictures which involved the proximal penile and distal bulbar urethra. Patients with low grade strictures involving the entire penile and bulbar urethra were classified as pan-urethral. After initial treatment for urethral stricture disease, the patients were followed up clinically. Functional success is assigned if the patient reported an improvement in voiding and the absence of symptoms of urinary obstruction. When a patient presented with obstructive lower urinary tract symptoms suggestive of recurrence, a follow-up RGU was done. Treatment failure was defined as the need for any secondary urethral intervention, such as DVIU or the need for urethroplasty.

Statistical analysis

The Kaplan-Meier estimator was used to estimate failure-specific success rates. Intervention-free times were measured in months and were censored at the date of the patient developing stricture recurrence. The statistical analyses were done utilising the non-parametric Mann-Whitney U-test to compare median lengths. The student's t-test and chi-squared test were used to compare baseline characteristics of patients. Differences where $p < 0.05$, were regarded as significant. All calculations were carried out with SPSS release 15.0 (SPSS Inc. Chicago, IL, USA).

Results

Three hundred and eight patients had complete records and were included in this retrospective study. The median age was forty-eight years (range 16–95 years), while the mean stricture length was 2.1 cm (range 0.2 cm to 10 cm). The findings with regard to age, symptoms and stricture characteristics are summarised in Table 3.1. The success rates for first procedures according to age groups did not differ significantly between age groups [53.3% of the patients aged 19–39 years, 41.3% aged 40–59 years, and 45.0% aged 60 years and older. ($p=0.202$)] (Table 3.1). The majority of patients ($n=200$; 64.9%)

presented with acute urinary retention secondary to an obliterated or near-obliterated urethral lumen. The overall success rates and stricture-free rates were similar for both obliterative and non-obliterated urethral lumens. (Table 3.1, log rank=0.942). Infective urethral stricture disease (USD) secondary to sexually transmitted diseases was the cause of stricture formation in the majority of patients (n=249; 81%). These patients presented with a positive history of urethritis and received treatment for a thick purulent urethral discharge for gonococcal urethritis. The difference between the success rates of first procedures in patients with infective USD (42.6%) versus those with traumatic USD (72.0%) was significantly different (p=0.019; HR 2.6; 95% CI 1.225–5.597), although the sample sizes were skewed.

The mean stricture length of infective urethral strictures was 2.3 cm (range 0.2 cm to 10 cm), significantly longer than that of traumatic strictures with a mean length of 1.5 cm (range 0.5 cm to 3.5 cm; p=0.001; 95% CI 0.2400–1.2557). With regard to stricture location the success rate of first procedures was not significantly different for bulbar, peno-bulbar and penile positions (p=0.870, Table 3.1). Strictures \geq 3 cm had a significantly worse outcome (p=0.008, Table 3.1).

Table 3.1 Age, presenting symptoms, aetiology and stricture characteristics of patients with urethral strictures (n=308).

Variable	Subgroup	Patients		Success rate		p-value Sub group analysis	p-value
		%	n	%	n		
Age (years)	19–39	26.6	88	53.4	47	0.202	
	40–59	44.8	138	41.3	57		
	≥ 60	26.0	80	45.0	36		
Presenting symptoms	LUTSa	28.6	88	46.6	41	0.606	
	AURb	64.9	200	46.5	93		
	Perineum sepsis	6.5	20	35.0	7		
Aetiology	Infection	80.8	249	42.6	106	0.005	0.037
	Trauma	8.1	25	72.0	18		
	Catheter-related	5.8	18	50	9		
	Unknown	5.2	16	50	8		
Location	Penile	8.1	25	44.0	11	0.870	
	Penobulbar	36.4	112	48.2	54		
	Bulbar	45.1	139	49.6	69		
Length (cm)	0.1–0.9 (mean 0.55)	26.0	80	56.3	45	0.008	0.010
	1.0–1.9 (mean 1.25)	29.9	92	44.6	41		
	2.0–2.9 (mean 2.16)	18.8	58	53.4	31		
	≥ 3.0 (mean 5.3)	25.3	78	30.8	24		

^aLUTS = lower urinary tract symptoms with non obliterative lumen; ^bAUR = acute urinary retention secondary to an obliterative lumen.

The overall outcomes per procedure are presented in table 3.2. First procedures were successful in 141 (45.8%) patients with urethral stricture. The long-term outcomes after first procedure demonstrated a high failure rate in the DVIU, ventral BMG and cPFU groups, requiring re-intervention compared to AR, AAR and dorsal BMGU.

Table 3.2 The outcome of first procedures at seven-year follow-up in patients with urethral strictures (n=308).

First procedure	Number of patients	Success rate of procedure		p-value: comparison between procedures	Median stricture length (cm)	Time to failure (months)	
		n	%				
DVIU	60	17	28.3%	0.0793	0.90	14.9	1.1-8
DVIU + Dilatation	87	37	42.5%		1.20	14.5	0.6–61.8
AR	98	57	58.2%	0.1790	1.50	15.5	0.8–62.3
AAR	10	8	80.0%		2.35	18.8	5.8–31.8
Dorsal BMGU	20	13	65.0%	0.0443	4.25	8.2	2.9–26.6
Ventral BMGU	11	3	27.3%		3.50	10.9	1.1–44.5
cPFU	16	2	12.5%	0.001•	5.00	12.9	1.7–72

*cPVU compared to Dorsal BMGU; AAR = augmented anastomotic urethroplasty; AR = anastomotic urethroplasty; BMGU = buccal mucosa graft urethroplasty; cPFU = circular penile skin flap urethroplasty; DIL = dilatation; DVIU = direct vision internal urethrotomy.

Table 3.3 Comparing the median stricture lengths between successful and failed procedures.

Procedure	Successful procedure median length and range in cm	Failed Procedure median length and range in cm	p-value	Median difference	95% Confidence interval for median difference
DVIU	0.5 (0.3 - 2.4)	1.0 (0.3 – 7.0)	0.0006	0.5	0.200 - 1.00
DVIU + Dilatation	1.0 (0.2 – 7.0)	1.5 (0.3 – 7.0)	0.0848	0.4	0.000 - 0.800
AR	1.5 (0.5 – 3.0)	1.5 (0.3 – 7.0)	0.0783	0.2	0.000 - 0.500
AAR	2.1 (1.0 – 6.0)	5.3 (4.5 – 6.0)	0.0896	3.3	Not estimable

The statistical analyses were done utilising the non-parametric Mann-Whitney U-test. AAR = augmented anastomotic urethroplasty; AR = anastomotic urethroplasty; DIL = dilatation; DVIU = direct vision internal urethrotomy.

Comparison between outcomes of different surgical procedures

Direct vision internal urethrotomy (DVIU) alone and combined with urethral dilatations (DVIU+Dil): DVIU started failing at a mean time of 14.9 months (range 1.1 to 84 months) after the procedure. The one-year stricture-free survival rate was 50%, which deteriorated to 16% at six years. The success rate of DVIU increased from 28.3% to 43% when combined with follow-up urethral dilatations. However, this increase was not statically

significant with a calculated p-value of 0.079 (Table 3.2). The stricture recurrence rate was thus slower when adjunct urethral dilatations were done after DVIU compared to DVIU alone (HR 1.4: 95% CI, 0.910 – 2.159).

Anastomotic urethroplasty (AR) was successful in 59% (58/99) of patients as a first procedure after seven years' follow-up. AR as first procedure failed at a mean of 15.5 months (range 0.8 to 62.2 months). The stricture-free rate was 75% at 12-months follow-up and decreased to 58% at eighty-four months.

Augmented anastomotic urethroplasty (AAR) was augmented with a dorsal buccal mucosa graft (BMG) with a success rate of 80% in ten patients who had a mean stricture length of 3.06 cm (range 1 cm to 6 cm). The mean time to stricture recurrence for AAR was 18.2 months (Table 3.2).

Substitution urethroplast; the dorsal buccal mucosa graft on-lay urethroplasty (DBMGU) had a success rate of 65% in twenty patients with a median stricture length of 4.25 cm (range 1.1 cm to 10 cm). The dorsal BMG on-lay had a higher success rate compared to the success rate of 27% in eleven patients who underwent the ventral buccal mucosa on-lay urethroplasty (VBMGU) however, there was a difference in stricture lengths ($p=0.044$; Table 3.2). Dorsal BMG on-lay urethroplasty had a higher success rate (65%) compared to the circular pedicled penile skin urethroplasty (cPFU) success rate of 13% ($p=0.001$; Table 3.2). The respective median stricture lengths were 4.25 cm and 5.0 cm. The mean time to stricture for dorsal BMG on-lay urethroplasty was 8.1 months, 10.8 months for ventral BMG on-lay, and 12.8 months for PFU (Figure 3.1). The stricture-free rates of dorsal BMG on-lay urethroplasty was higher than both ventral BMG on-lay and cPFU after 24 months' follow-up (Figure 3.1).

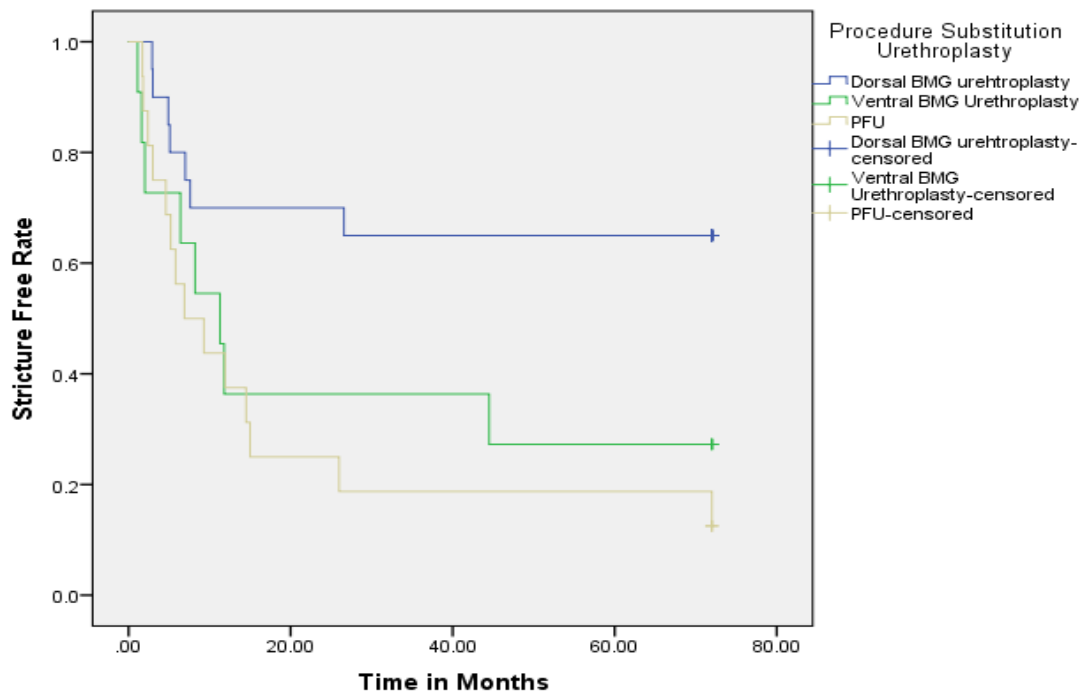
The relation between procedures and stricture lengths are depicted in Table 3.3. The median stricture lengths were significantly longer in patients who had failed DVIU with a difference that range between 0.2 cm to 1.0 cm ($p = 0.0006$; Table 3.3). There was no significant difference in stricture lengths between failed and successful patients who had DVIU+DIL, AAR, DBMGU and cPFU (Tables 3.3 and 3.4).

Table 3.4 Comparing the median stricture lengths between successful and failed substitution urethroplasty procedures.

Procedure	Successful procedure median length and range in cm	Failed procedure median length and range in cm	p value	Median difference	95% Confidence interval for median difference
DBMGU	4.0 (2.0 – 7.0)	5.5 (1.1 – 10.0)	0.1535	1.5	-0.900 - 3.500
VBMGU	2.0 (0.8 – 2.5)	3.75 (1.0 – 4.5)	0.0408	1.75	Not estimable
cPFU	3.5 (2.0 – 5.0)	5.0 (2.0 – 7.0)	0.2611	1.35	Not estimable

The statistical analyses were done utilising the non-parametric Mann-Whitney U-test. DBMGU = Dorsal buccal mucosa urethroplasty: VBMGU = Ventral buccal mucosa on-lay cPFU = circular penile flap urethroplasty.

Stricture free rates of substitution urethroplasty



Success rate (%)	Time in months			p-value
	6 months	12 months	24 months	
DBMGU	80	70	65	0.031
VBMGU	64	36	36	
cPFU	56	38	18	

Figure 3.1. The stricture free rates of substitution urethroplasty.

DBMGU = Dorsal buccal mucosa urethroplasty: VBMGU = Ventral buccal mucosa on-lay cPFU = circular penile flap urethroplasty.

Discussion

This retrospective analytical cohort study demonstrates the important relationships between aetiology, underlying pathology and length of obstruction and the various surgical procedures in a developing world population.

Aetiology and length: 81% of cases presented after infective urethritis. Importantly, it demonstrates that infective urethral strictures lengths were significantly longer than that of traumatic strictures. This is supported by the literature where Palminteri *et al.*, (2013) reported that inflammatory strictures secondary to lichen sclerosis are longer than other etiologies. Aetiology clearly has an influence on success rates of endoscopic and urethroplasties, demonstrated by the overall significantly lower success rates for infection related strictures compared to that of trauma related strictures in this study.⁵ This is supported by a multi-variant analysis by Han *et al.* (2015), who found infectious aetiology to be associated with stricture recurrence. Chapple *et al.* (2014), also showed that inflammatory strictures have a tendency to be longer and have more extensive underlying spongiofibrosis. This central South African study showed that the re-stricture rate was 2.6 times higher in patients with infective strictures, compared to patients with trauma related urethral strictures and post-inflammatory urethral strictures had higher revision rates in the first eighteen months (Roehrborn *et al.*, 1994, Chapple *et al.*, 2014).

An important and very likely explanation is that the stricture lengths were underestimated with RGU as the only imaging approach. RGU is limited in determining the stricture length because it cannot determine the extent of the fibrosis. Ultrasonography as an adjunctive investigation would demonstrate the extent of the fibrosis, thus determine the correct stricture length accurately (Buckley *et al.*, 2011).

Procedures: The disappointing results of DVIU probably relate to this and although DVIU with serial dilatation has slightly better results, it is questionable whether these procedures should be attempted beyond 1.0 cm lesions (very short) and importantly confirmed pre-procedure by sonography.

In this study, the AR cohort had a long-term success rate of only 58%, much lower than the reported 99% by Elthaway *et al.* (2007) in their series of 260 patients. Da Silva *et al.*

(2008), did biopsies of the normal appearing ends after the urethral stricture was excised before an end to end anastomosis was done in twenty-nine patients with bulbar urethral strictures. They found in all their patients histological evidence of chronic and acute inflammatory changes in the normal appearing urethral ends. This study points out that the length of inflammatory strictures was underestimated on appearance and may be an important cause of stricture recurrence.

The AAR cohort appears to be superior to AR in this study and a possible explanation is that the augmentation of the anastomosis with a BMG compensates for underestimated stricture length in inflammatory strictures.

No significant difference in success rates of end-to-end anastomosis strictures shorter than 2 cm compared to strictures longer than 2 cm could be demonstrated by *Barbagli et al. (2007)*. Success rates of 87.6% have been reported when anastomotic urethroplasty was done for strictures with a mean length of 3.1 cm (*Aghaji et al., 2001*). In this study, stricture lengths longer than 3 cm for the AR procedure had a poor outcome with a success rate of only 11%. This might once again be attributed to the underestimation of the extent of the actual pathology by RGU alone. The advantage of AAR is that the worst part of the urethra can be excised, limiting the graft size and reducing the risk of urethroplasty failure. (*Levine et al., 2007*). The success rate of 80% with AAR augmented with a dorsal BMG in this study compares favorably to the 79.2%, 93% and 96,6% success rate reported previously (*Barbagli et al., 2008, Guralnick et al., 2001, Hoy et al., 2013*).

Barbagli et al. (2005), proposes that when the stricture is longer than 3 cm, substitution urethroplasty should be the proposed approach, followed by BMG placed dorsal, ventral or lateral.

The placement of the graft dorsal or ventral is a contentious issue when doing substitution urethroplasty, with no difference in success rate reported in the literature (*Vasudeva et al., 2015*). *Vasudeva et al. (2015)* reported similar success rates – 92.5% vs. 90% for dorsal and ventral BMGU in their prospective randomised study respectively. This was also the finding of *Barbagli et al. (2005)* when comparing the placement of the buccal

mucosa graft dorsal, ventral or lateral with similar success rates of 83% vs. 85%. They concluded that the treatment outcome was not affected by surgical technique. It is important to note in the above studies that the aetiology of urethral strictures in the prospective study of Vasudeva *et al.* (2015) was iatrogenic and in the study of Barbagli *et al.* (2005) mainly traumatic. In contrast, the dorsal BMG on-lay urethroplasty cohort had a markedly higher success rate compared to the ventrally-placed BMG cohort, 65% and 27.3% respectively, at seven years in this follow-up study where aetiology was inflammatory in the vast majority of patients.

The VBMGU cohort in this study had a much lower success rate when compared to the literature. The success rate for the ventral BMG on-lay in a series of 214 men was 86% (Barbagli *et al.* 2013). It is known that substitution urethroplasty deteriorates over time with failure rates of 50% at fifteen years (Andrich *et al.*, 2003). This study demonstrates a high re-stricture rate in the first eighteen months after urethroplasty. Only eleven patients were managed by VBMGU, which might represent a learning curve. It also remains to speculate what role is played by the underlying inflammatory process in determining the outcome of this procedure.

Type of stricture: The majority of patients (65%) in this study had obliterative strictures. Treatment outcome was the same when comparing obliterated strictures with non-obliterative strictures. From this study it can be concluded that obliterative urethral lumens played no role in the complexity of urethral strictures when urethroplasty was done, because the obliterative lumen was excised or augmented to a good calibre. It is important to note that obliterative urethral lumens were also excluded from the urethral stricture score (U-score) validation (Eswara *et al.*, 2015).

Location of Stricture: With regard to stricture location, the success rate of first procedures was not significantly different for bulbar, peno-bulbar and penile positions.

An important controversy in substitution urethroplasty is the use of grafts versus flaps with equal reported outcomes of BMG (90%), versus penile skin flap (86%) in a prospective randomised trial (Dubey *et al.*, 2007). However, in this study the dorsal BMG had a higher success rate (65%), compared with the PFU (13%) for mean stricture lengths of 4.7 cm

and 4.8 cm respectively. The cPFU cohort re-stricture rate was higher compared to the other substitution urethroplasties. There are conflicting data when comparing BMG with FCFs, where authors reported that grafts have higher success rates (80%) than flaps (67%). However, no differences in outcome have also been reported (Barbagli *et al.*, 2008, Levine *et al.*, 2007, Dubey *et al.*, 2007). The overall success rates were not affected by stricture location, except in those patients with low-grade diffuse urethral disease (panurethral). However, the stricture recurrence rate, according to a meta-analysis, was the lowest for bulbar strictures compared to that of penile strictures (Meeks *et al.*, 2009).

Limitations

This is a retrospective study and procedures were performed by different surgeons in a training institution. The routine use of sonography was not available in the study period, which could have attributed to the underestimation of stricture length. Recurrence was clinically defined when a patient presented with voiding problems on follow-up, at which stage a RGU was performed. The results may provide guidance for duration and intensity of postoperative surveillance as well as the need to develop a standardised protocol for inflammatory urethral strictures. We emphasize the importance to follow patients up for longer than five years and counsel them accordingly.

Conclusion

Treatment failure was higher in infective urethral strictures than that of trauma-related strictures. The significant decrease in stricture-free survival in the first eighteen months is noteworthy and could possibly have contributed to the infective nature of the strictures and an ongoing inflammatory process. The role of re-infection should also be determined. It is imperative that stricture length be determined by routine sonography and possibly MRI, in order to accurately determine the length of obstruction. Stricture location had no negative effect on the treatment outcome. AR could be performed successfully for stricture lengths of 2 cm and shorter. The use of AAR in inflammatory cases should probably be restricted to stricture length up to 3 cm and should be further investigated. Dorsal placement of the BMG rather than ventral had significantly better outcomes in a small group of patients. Circular PFU had a poor long-term outcome in this study and a two-stage procedure should probably be considered in similar centres.

Conflict of interest

The authors have no conflict of interest to declare.

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Chapter 4

ARTICLE 2

Anastomotic urethroplasty with double layer continuous running suture re-anastomosis versus interrupted suture re-anastomosis for infective bulbar urethral strictures: A prospective randomised trial

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Abstract

Introduction: The objective of this study was to compare a double layer continuous running suture re-anastomosis urethral stricture repair with early catheter removal to the conventional interrupted suture re-anastomosis after excision of a bulbar urethral stricture.

Methods: Thirty-six patients were randomised in two groups with bulbar urethral strictures of 2.5 cm and shorter. Group 1 included nineteen patients with a mean stricture length of 1.20 cm who underwent the double layer continuous running suture re-anastomosis after excision of the bulbar stricture. The catheters of the patients in Group 1 were removed within twenty-four hours after urethroplasty. Group 2 included seventeen patients with a mean stricture length of 1.27 cm who underwent the conventional interrupted suture re-anastomosis. The catheters in Group 2 were removed fourteen days after urethroplasty. Outcomes were based on retrograde urography (RGU) performed on the first post-operative day in Group 1 and in both groups (Group 1 and Group 2) at six-weeks post-surgery. The patients were followed up for a minimum of eighteen months and longer. Success was defined as no need for subsequent dilatation, direct vision internal urethrotomy (DVIU) or urethroplasty required to treat the urethral stricture.

Results: A total of thirty-six patients (mean age 45.5 years, range 20 to 69 years) with bulbar urethral strictures were included in this study. The average stricture lengths were comparable between the two groups according to the retrograde urethrogram: 1.20 cm (range 0.6cm to 2 cm) in Group 1 and 1.27 cm (range 0.5 cm to 2.4 cm in Group 2 respectively ($p=0.631$). The success rate for Group 1 was 90% after a mean follow-up of thirty-six months (range 20 to 40 months), clinically significant compared to the 71% in Group 2 after a mean follow-up of thirty-three months (range 19 to 40 months) [$p = 0.218$, 95% CI: 0.462 – 41.5766].

Conclusions: Anastomotic urethroplasty (AR) performed with a double layer re-anastomosis had a cure rate comparable to the conventional anastomosis with interrupted sutures after a follow-up of eighteen months and longer. The urethral catheter can be safely removed within twenty-four hours after excision of stricture and double layer re-anastomosis.

Key words: Urethral stricture, anastomotic urethroplasty, bulbar urethral stricture.

Introduction

The end to end anastomosis for bulbar urethral strictures has set a gold standard for strictures less than 2 cm (Barbagli *et al.*, 2007). Anastomotic urethroplasty yields good results for iatrogenic or instrument related bulbar urethral strictures shorter than 2 cm, with a reported success rate of approximately 95% (Santucci *et al.*, 2002). Elthahawy *et al.* (2007), report a success rate of 99% in a series of 260 patients who underwent

anastomotic urethroplasty for traumatic and instrument related strictures. One of the advantages of the anastomotic urethroplasty is that patients can be discharged early post-operatively, even as a same day procedure (MacDonald *et al.* 2005). This surgical technique involves using a watertight double layer continuous running suture re-anastomosis and the removal of the urethral catheter upon discharge on day one post-operatively. The early removal of the urethral catheter may decrease catheter related problems, such as urinary tract infections and possible pressure necrosis of urethral epithelium, which increase the risk for re-stricturing (Biering-Sørensen *et al.*, 1999). The aim of this study was to compare the outcomes of the double layer continuous running suture anastomosis with early catheter removal to the conventional interrupted suture technique with fourteen-day catheterisation in a prospective randomised study during an eighteen-month follow-up period.

Methodology

Thirty-six patients with bulbar urethral strictures were sequentially randomised into two groups. The preoperative evaluation included clinical history, physical examination and urine analysis. All patients underwent a retrograde urethrogram (RGU) to determine the length and position of the urethral stricture. The RGU was performed using a clamp method with drip infusion as described in literature (Berna-Serná, *et al.*, 1999) The inclusion criteria were stricture lengths of 2.5 cm and shorter, located in the bulbar urethra. Patients who had had one direct vision internal urethrotomy (DVIU) were included. Patients who had had two and more DVIU's and previous urethroplasty failures were excluded from this study.

The patients were allocated to the groups according to their arrival at the clinic; that is all uneven numbers were allocated to Group 1 and even numbers to Group 2. A prophylactic broad-spectrum antibiotic namely ceftriaxone, was administered preoperatively.

All the surgical procedures were performed under general anaesthesia. The patients were placed in the lithotomy position and the urethra approached through a perineum incision over the length of the urethral stricture splitting the corpus spongiosum muscle. The urethra was probed with a 16Fr catheter to determine the location of the stricture and then mobilised from the corpora cavernosum and transected in the stricture site. The urethral

stricture was excised and the healthy urethral ends sutured with 4/0 Vicral continuous running sutures in double layers in Group 1 (Figures 4.1 and 4.2). The double layer continuous running suture 4/0 Vicral re-anastomosis was performed by first suturing the urethral mucosa, starting from a 12 o'clock position with two sutures closed in a running fashion clockwise and anti-clockwise to the 6 o'clock position. The spongiosum was then sutured with two 4/0 vicral sutures starting with two sutures at the 12 o'clock position, closing it running fashion clockwise and anti-clockwise to the 6 o'clock position (Figures 4.1 and 4.2). The anastomosis after stricture excision in patients of Group 2 was done with five interrupted sutures incorporating the epithelium and spongiosum with 3/0 Vicral sutures (Figure 4.3).

After the anastomosis was completed, the bulbospongiosum muscle was closed over the urethra with a 4/0 vicral suture and the skin was then closed with a 3/0 vicral running suture in both groups.

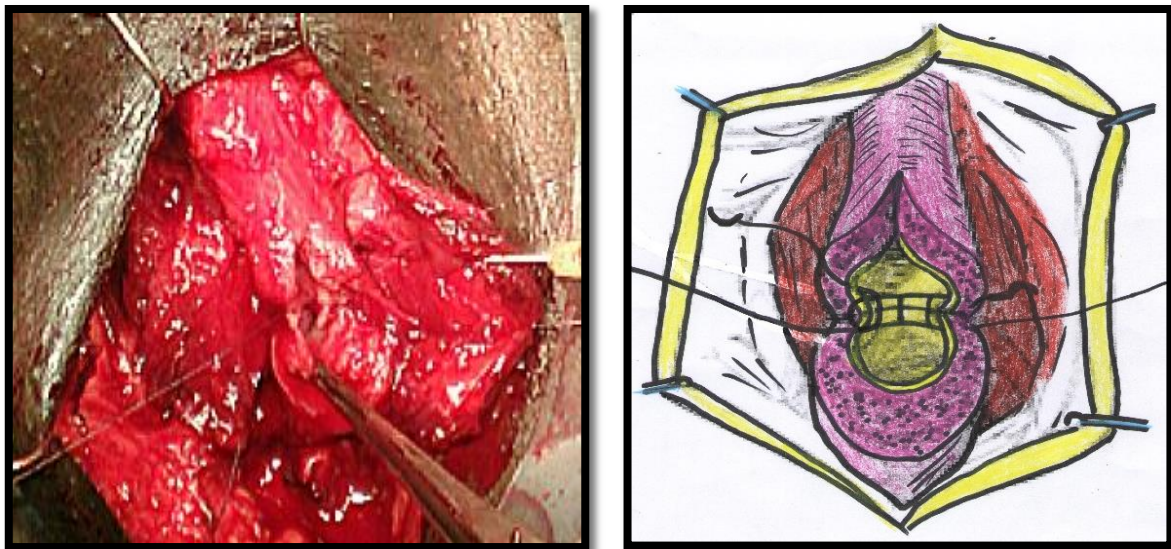


Figure 4.1. The urethral epithelium sutured with a continuous running suture and the spongiosum sutured in the same fashion separately.

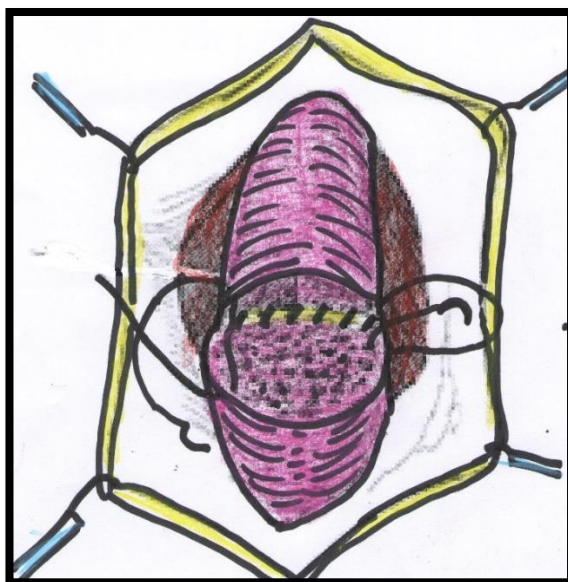


Figure 4.2. Closing of the spongiosum with a running suture.

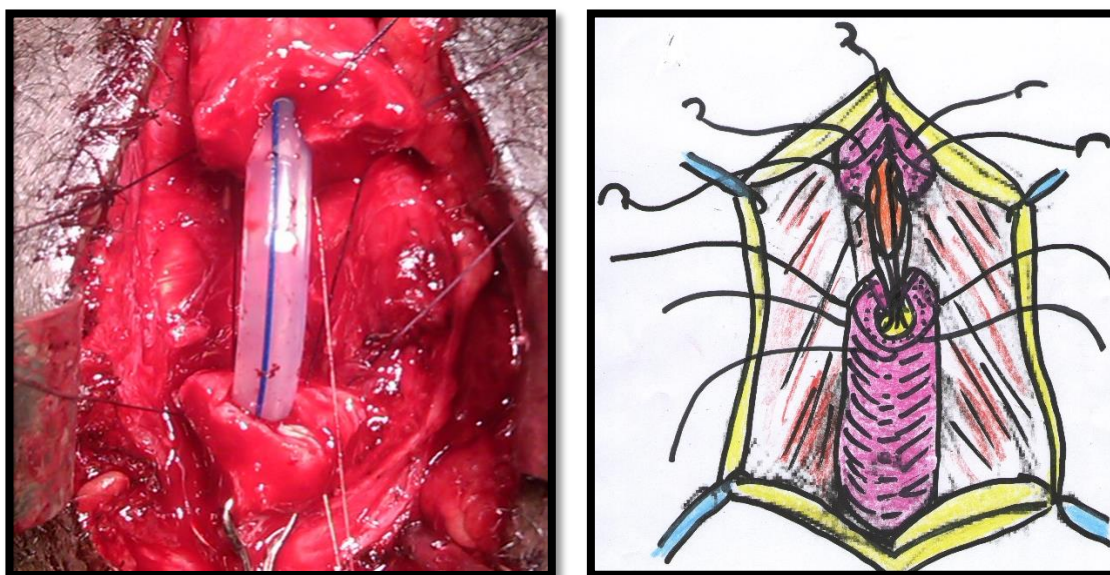


Figure 4.3. The anastomosis is done with five interrupted sutures incorporating the epithelium and spongiosum.

Group 1 consisted of nineteen patients (n=19) and Group 2 of seventeen patients after two patients were lost during randomisation. The urethral catheters of patients in Group 1 were removed on day one and after fourteen days in Group 2. After urethroplasty A RUG was done at the time of catheter removal and contrast extravasation was documented when noted. All patients were seen and had a follow-up RGU at six weeks post-operatively. Patients in Group 1 were discharged on day one with saline sitz baths

and oral analgesics after their catheters had been removed. The catheters in Group 2 were removed on post-operative day fourteen. All patients were then followed up three-monthly for eighteen months with a detailed history of urethral stricture recurrence. Success was defined as having no need for subsequent dilatation, DVIU or urethroplasty to treat the urethral stricture.

Statistical analysis

The Student's test was used to compare age and length. Categorical data were analysed with the chi-squared test and the Fisher's exact test. Differences were regarded as significant with $p \leq 0.05$. All calculations were done with SPSS® release 15. (SPSS Inc, Chicago, IL, USA).

Results

A total of thirty-six patients with a mean age of 45.5 years (range 20 to 69 years) with bulbar urethral strictures were included in this study. All patients had a history of purulent urethral discharge. Five patients were treated for gonococcal infection in other centres before referral and thirty-one patients were diagnosed and treated for confirmed gonococcal infection at our institution.

Stricture lengths by RGU were 1.20 cm (range 0.6 cm to 2 cm) in Group 1 and 1.27 cm (range 0.5 cm to 2.4 cm) in Group 2 respectively ($p=0.631$)(Table 4.1). The overall success rate after an eighteen-month minimum follow-up period for Group 1 was 90% compared to the 71% in Group 2 [$p=0.2185$; CI (95%): 0.4628 to 41.5756].

Table 4.1: Summary of results of Group 1 patients who had the continuous double layer re-anastomosis and Group 2 patients who had interrupted suture re-anastomosis.

Variable	Group 1 (n=19)	Group 2 (n=17)	p-value
Mean age (years)	46.05	45.05	0.822
Mean stricture length (cm)	1.20	1.27	0.631
Success rate (%)	90%	71%	0.219
Time to fail (mean in months)	4.9 (3.6 and 6.2)	5.6 (1.1 to 10.1)	0.804
Mean follow-up (months)	36 (20 to 40)	33 (19 to 41)	0.716

The RGU performed at the time of catheter removal of patients in Group 1 on day one, demonstrated minimal extravasation but with no voiding difficulty in six patients (32%). These patients were discharged from the hospital without reinserting a Foley catheter. The extravasation cleared up spontaneously when patients had follow-up RGU's six weeks after catheter removal (Figures 4.4 and 4.5). Patients with extravasation had no difficulty with excessive perineum swelling. The patients in Group 2 had their urethral catheters removed two weeks post-surgery and an RGU was performed at six weeks after catheter removal. In two patients of Group 1 stricture recurrence occurred at an average of 4.9 months (3.6 and 6.2 months). The seven failures in Group 2 occurred at an average of 5.6 months (range 1.1 to 10.1 months) ($p=0.804$).

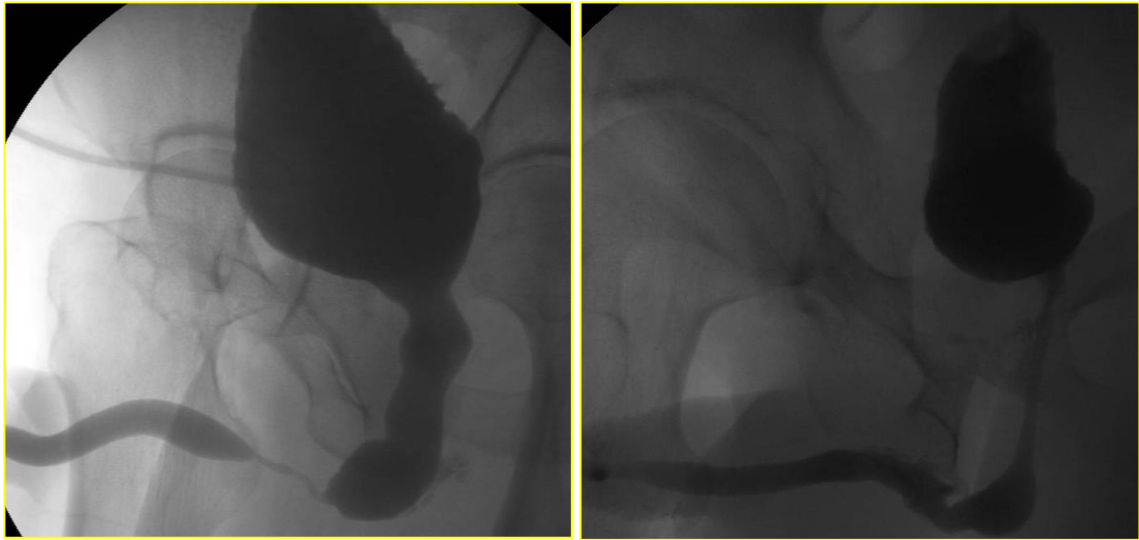


Figure 4.4. Retrograde urethrogram in a patient with a 2.1 cm stricture pre and 24-hour post double layer continuous running suture re-anastomosis.

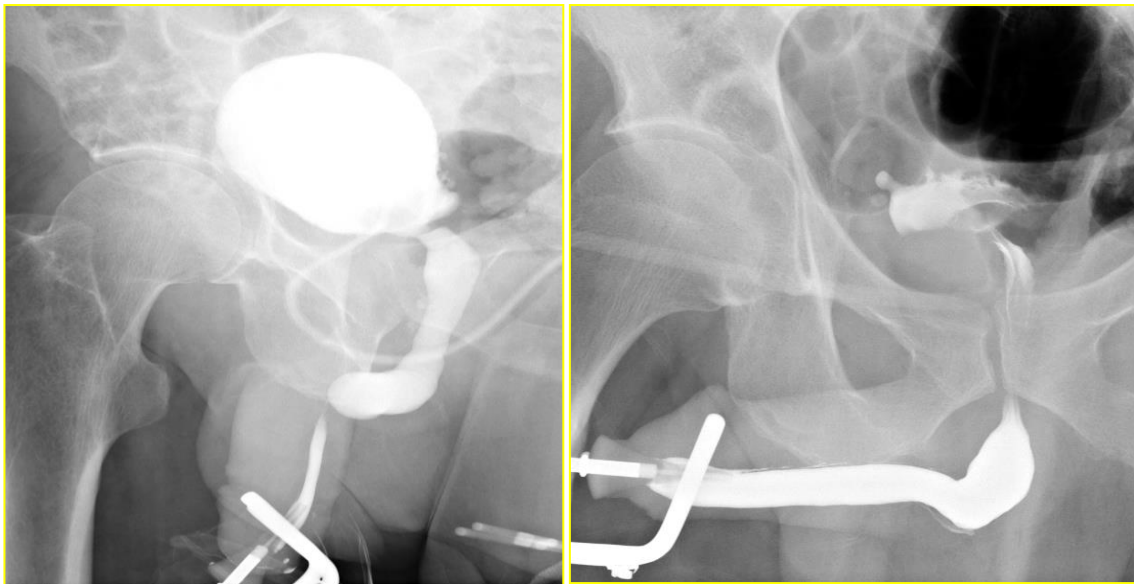


Figure 4.5. Retrograde urethrogram in a patient with 0.8 cm stricture pre and 24-hour post double layer continuous running suture re-anastomosis.

Discussion

This study demonstrated that a short hospital stay with catheter removal on day one is feasible when performing a double continuous running suture anastomotic urethroplasty. The anastomosis in two layers ensured that the patients could go home within one day without urethral catheter with a success rate of 90%, which was not inferior to the success

rate of 71% when the anastomosis was done with interrupted sutures. Theoretically, the short catheterisation period limits the risk of reduced blood flow and pressure induced necrosis that may be caused by the urethral catheter. This study confirmed that the early catheter removal has no deleterious effect on the anastomotic urethroplasty outcome. In previous studies catheterisation for seven to twenty-one days is recommended for anastomotic urethroplasty, although three days appear to be adequate. Interestingly, the 24-hour post-RGU exhibited urine extravasation in 67% or six out of nine patients (Gallentine *et al.*, 2002).

The reason why an indwelling urethral catheter is routinely used is to allow for complete mucosal coaptation in the area of repair. However, a catheter may also at the same time prevent mucosal cross-healing and urethral distension during voiding. It is possible that if urine traverses the suture line into the surrounding tissue, patients can develop urinomas with fistula formation (Gallentine *et al.*, 2002, Kawashima *et al.*, 2004). The extravasation of urine on the twenty-four-hour post-operative RGU was limited in the patients of this study and importantly, they did not develop any complications. A possible explanation for the absence of urinoma formation secondary to the urine extravasation might be the patent urethra. A patent urethra ensures that pressure on the suture line is limited and healing of the anastomosis area is mostly pressure free except during voiding. Other studies with the two-layer anastomosis technique also reported low urine extravasation of three percent when performing early postoperative voiding cystourethrography (VCUG) (Terlecki *et al.*, 2011). Pericatheter RGU has been recommended to avoid premature catheter removal and subsequent catheterisation with unnecessary urethral manipulation (Graneri *et al.*, 2014, Solanki *et al.*, 2014, Aghaji *et al.*, 2001). This study demonstrates that reinsertion of the Foleys catheter may not be required in a patent urethra with limited extravasation.

As stricture length is a contentious issue in anastomotic urethroplasty, only patients who had strictures shorter than 2.5 cm were included. However, Barbagli *et al.* (2007) could not find a statistical difference in success rates of end to end anastomosis in lengths less than 2 cm compared to lengths longer than 2 cm and Aghaji *et al.* (2001), reported a success rate of 88 % in their group of 98 patients with a mean length of 3.1 cm.

Patients who had one DVIU were included in this study. It has to be noted that it has been demonstrated that previously failed DVIU had no negative impact on the outcome of

subsequent urethroplasty (Barbagli *et al.*, 2001). Also, multiple failed attempts of dilatation and/or DVIU did not impact on the outcome of anastomotic urethroplasty by Eltahawy *et al.* (2007). However, for this study, the admission criteria were restricted to one DVIU intervention, as failure rates of subsequent urethroplasties doubled when patients had previous manipulation for urethral stricture disease (Roehrborn *et al.*, 1994).

One patient in Group 2 developed symptoms of stricture recurrence within 1.1 month after urethroplasty due to a poor re-anastomosis technique. If this patient is excluded from the analyses, the success rate of 75% (12/16) does not change conclusions. Patients in this study were followed up for a minimum of eighteen months, although long term follow-up is necessary as success rates of anastomotic urethroplasty can decrease over time, regardless of technique (Andrich *et al.*, 2003).

Conclusion

Anastomotic urethroplasty performing a watertight double layer re-anastomosis with early catheter removal had a cure rate comparable to the conventional interrupted suture anastomosis with 14-day catheterisation. Although the sample size was small, the catheterisation removal on day one after anastomotic urethroplasty appears to play no role in the outcome of anastomotic urethroplasty in Group 1. The presence of minimal extravasation cleared up without negatively influencing the success rate. Therefore, small amounts of contrast extravasation do not warrant reinsertion of the catheter as long as the patient has a patent urethra. In conclusion, the double layer continuous running suture re-anastomosis made early discharge and urethral catheter removal possible and is not associated with an increase in re-stricture formation in the short to medium term. This technique warrants further study with larger patient numbers and extended follow-up periods in patients with bulbar strictures up to 2,5 cm.

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Chapter 5

ARTICLE 3

A modified two-stage urethroplasty technique for inflammatory panurethral stricture management

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Abstract

Objective: Panurethral strictures with obliteration of the urethral lumen remain a surgical challenge. This case study reports on the outcomes of a two-stage urethroplasty technique where the fibrotic urethra was incorporated as part of the repair as described.

Methods: During the first stage, the urethra was mobilised from the corpora cavernosum, incised dorsally and ventrally without transection, in order to preserve the blood supply within the spongy tissue. The buccal mucosa graft, harvested from the inner cheek, was then quilted with Vicral 5/0 to the tunica albuginea of the corpora cavernosum. The dorsal halves of the urethra were sutured to the graft margins with Vicral 4/0 to create a urethral plate. A pedicled penile skin flap was created from the prepuce or penile skin and sutured to the ventral side of one of the halves of the urethra and penile skin to the other half. The catheter was removed seven days after the procedure. A second stage reconstruction was performed after six months, during which the lateral penile skin flaps on the ventral sides of the bivalved urethra were mobilised to close the urethra ventrally. The urethral catheter was removed four weeks after the second-stage procedure. Functional success was assigned when the patient reported an improvement in quality of life, was able to void without difficulty and producing an effective urinary stream. Failure of urethroplasty was defined as any need for postoperative imaging that necessitated a secondary procedure.

Results: The age of the seven patients varied between thirty-seven and forty-five years (average forty-four years). The mean stricture length was 7.1 cm (range 6.1 cm to 10.2 cm). Complications occurred in two patients: one suffered from an anastomotic stricture and the other from a urethra cutaneous fistula. The final success rate was 71% (five out of seven) at twenty-four months' follow-up.

Conclusion: Incorporating the fibrotic urethra as a modification to the two-stage repair strongly supports this particular procedure to treat panurethral strictures with obliterated lumens.

Keywords: Urethral stricture, panurethral stricture, two-stage urethroplasty.

Introduction

Long-segment urethral strictures involving the bulbar and pendulous urethra with an obliterated lumen remain a challenging surgical problem. Complex penile urethral strictures can be treated as a one-stage procedure. Tube augmentation with circumferential fasciocutaneous penile skin flaps, which carry its own blood supply has important potential value in the reconstruction of the urethra after excision of the diseased urethra (Xue *et al.*, 2016). Xue *et al.* (2016) report a success rate of 60% at three-year follow-up in patients with obliterative panurethral strictures treated with tubularised preputial or penile skin flap urethroplasty. A two-stage urethroplasty is indicated when a

urethral stricture is associated with unhealthy perineal scrotal skin, urethrocutaneous fistulae and fibrotic obliterated urethral lumens, which preclude standard reconstructive techniques. The two-stage Johanson procedure, with or without free graft, is the conventional technique applied in order to repair anterior panurethral strictures (Lapides,1959). Hair-growing scrotal and perineal skin can result in chronic urinary tract infections, lithogenesis, fistulation, and diverticulum formation of the reconstructed urethra. These are drawbacks of this approach, which have led to a modification of the Johanson technique. In this study the modification included the reconstruction of a neo urethra, which incorporates the fibrotic urethra and the combining of a dorsal onlay buccal mucosa graft (BMG) with ventral pedicled penile skin flaps as a two-stage procedure. The aim of this study was to determine whether this modification improved the outcomes of long-segment urethral stricture complications in patients.

Methodology

Study population

A case series involving seven men with inflammatory pan-urethral stricture (spanning over the bulbar and penile urethra), secondary to gonococcal infection and presenting with obliterated urethral lumens was completed. They had received treatment for purulent urethral discharge and according to their hospital records, clinical and laboratory diagnoses of gonococcal disease had been made. Pre-operatively the patients underwent retrograde combined with antegrade urethragrams to determine the length of the stricture (Figure 5.1a). At presentation, the patients underwent a cystoscopy and in the cases where the lumen could be canalised with guide wire, the patients were excluded. These patients were managed with a one-stage dorsal buccal mucosa graft (BMG) onlay urethroplasty at the Universitas hospital.

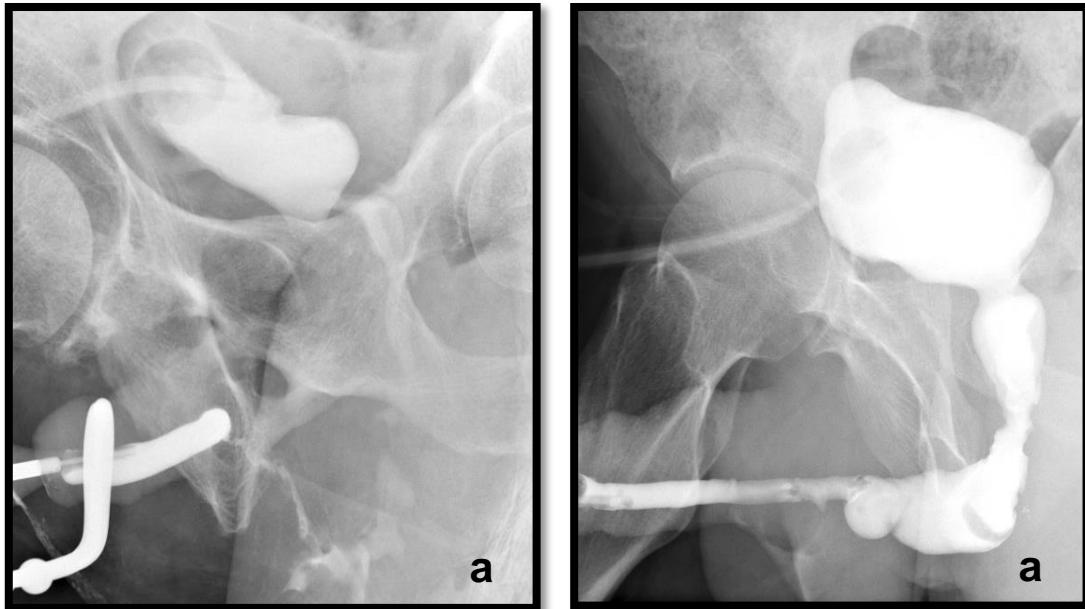


Figure 5.1. (a) Retrograde combined with antegrade urethrogram showing the obliterated urethral lumen with urethrocutaneous fistula. (b) Post repair complication in one patient with distal anastomotic stricture and diverticulum formation.

However, in patients where the lumen is obliterated this is not possible. Therefore, the seven patients underwent urethral reconstruction with dorsal buccal mucosa onlay combined with ventral pedicled penile skin flaps, incorporating the fibrotic urethra as a two-stage procedure. Follow-up was conducted on a three-monthly basis for twenty-four months.

The examination included assessment of symptoms that may suggest stricture recurrence, a physical examination as well as a urine analysis. Due to financial constraints, a retrograde urethrogram RUG was only done in case the patient complained of poor urine flow. Functional success was defined if the patient did not have obstructive voiding symptoms and gave a history of an improvement in his quality of life. Failure was defined as the need for imaging that led to any intervention that may be required during the twenty-four months of follow-up. Complications such as wound infections, urethrocutaneous fistula formation, urinary incontinence and post void dribbling were also documented.

Surgical procedure

During the first stage, patients were positioned in the lithotomy position. The urethra was exposed through a longitudinal ventral incision of the skin and dartos (Figures 5.2a and b).

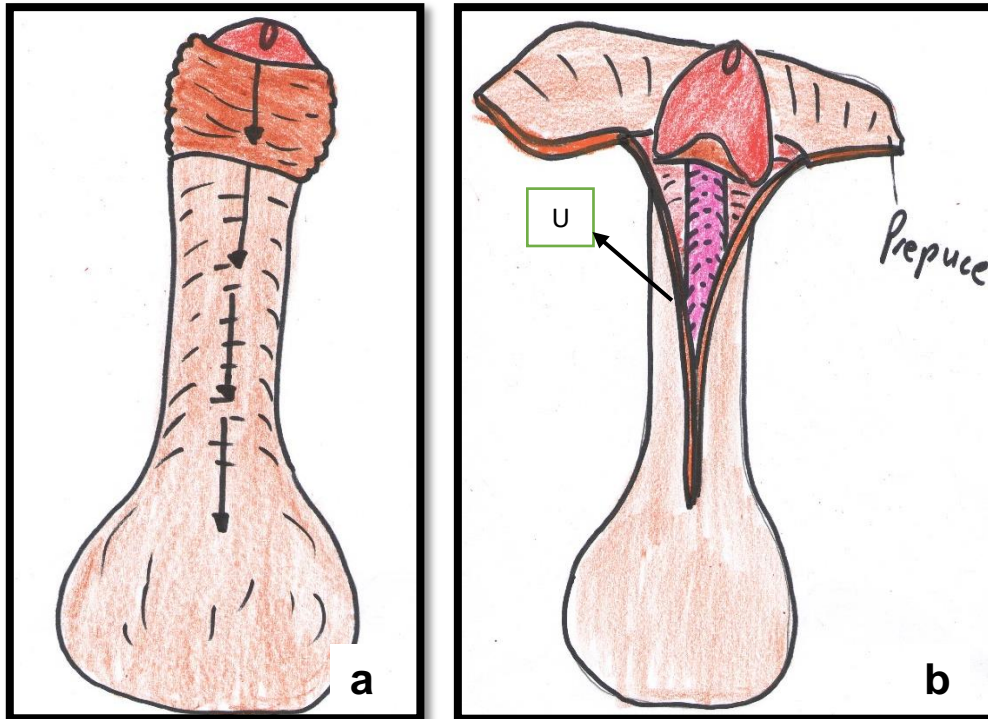


Figure 5.2. The penile skin is mobilised and split ventrally (a) onto the urethra (**U**) (b).

A large curved metal probe (20 F) was passed through the suprapubic catheter tract and bladder neck into the bulbar urethra to identify the proximal end of the stricture. Thereafter, the urethra was mobilised from the corpora cavernosum, incised dorsally and ventrally without transection in order to preserve the continuity of the blood supply within the spongy tissue (Figures 5.3a and b).

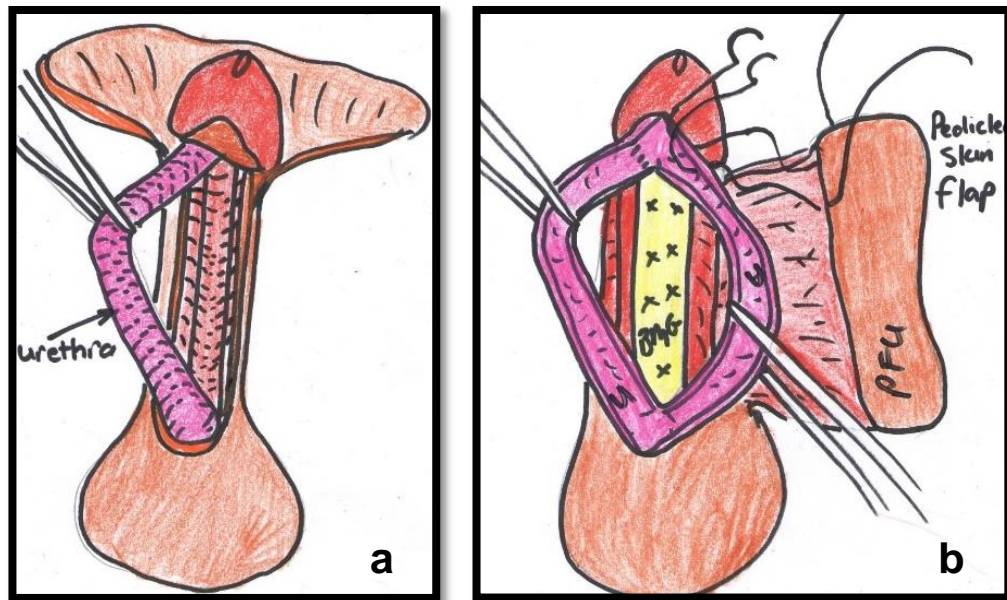


Figure 5.3. (a) Mobilise the urethra lengthwise from the corpora cavernosum and bivalve the urethra in length. (b) BMG is quilted to the corpora spongiosum and a pedicled penile skin flap created (PFU).

Depending on the size of the urethral reconstruction, one or several pieces of buccal mucosa were harvested, approximately 30% longer than the measured urethral stricture length. The preferred harvesting area was the inner cheek and both the left and right side were used, if necessary. The buccal mucosa graft was then quilted with Vicral 5/0 to the tunica albuginea of the corpora cavernosum and the dorsal halves of the urethra were sutured to the graft margins with Vicral 4/0 to create a urethral plate (Figures 5.4a and b).

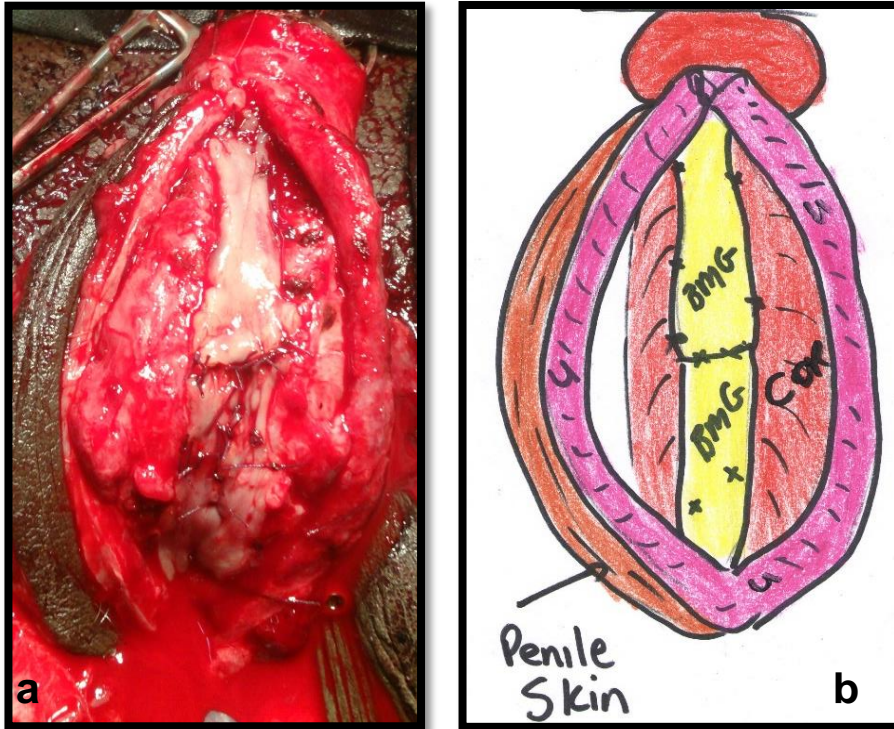


Figure 5.4. (a) BMG is quilted to the corpora cavernosum. (b) Schematic drawing. The dorsal sides of the bivalve urethra are then sutured to the BMG.

A pedicled penile skin flap was created from the prepuce or penile skin and sutured to the ventral side of one of the halves of the urethra and penile skin sutured to the other half (Figures 5.5a and b).

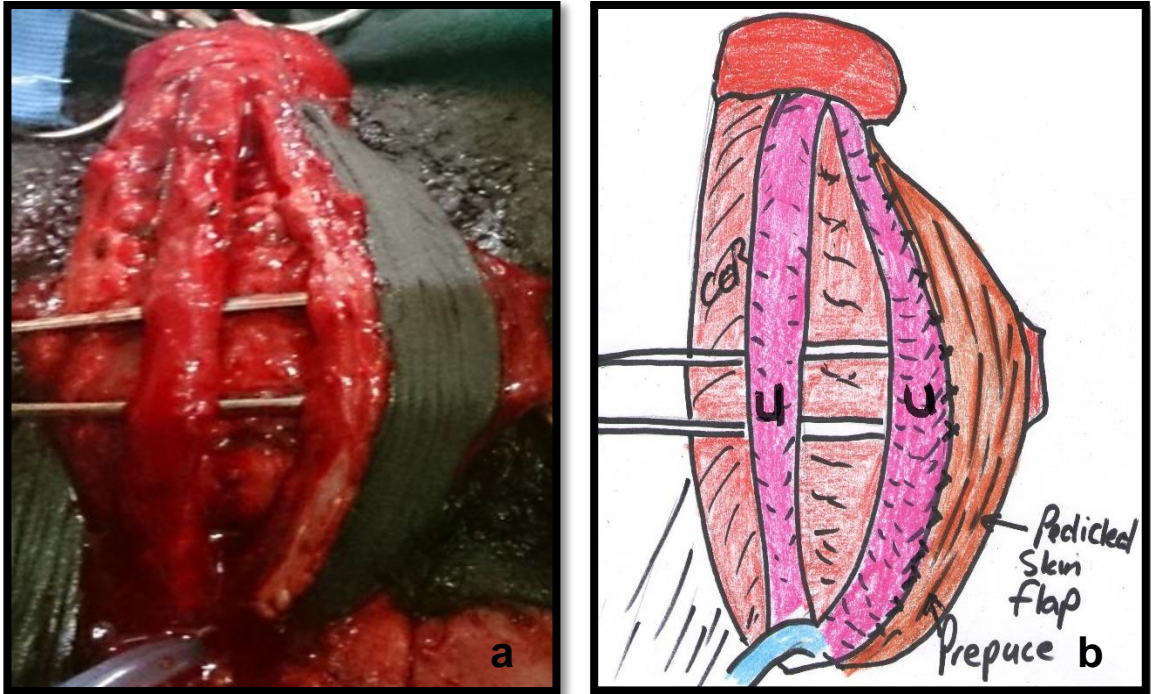


Figure 5.5. (a) Vascular pedicled penile skin flap (PFU) is created and sutured to the ventral side of one of the halves of the urethra. (b) Schematic drawing (cor = corpora; u = urethra).

The pedicled penile skin is vital in the second stage, where the neo-urethra will be created with non-hair bearing skin. The opened urethras were allowed to heal and mature over a period of six months (Figures 5.6a and b).

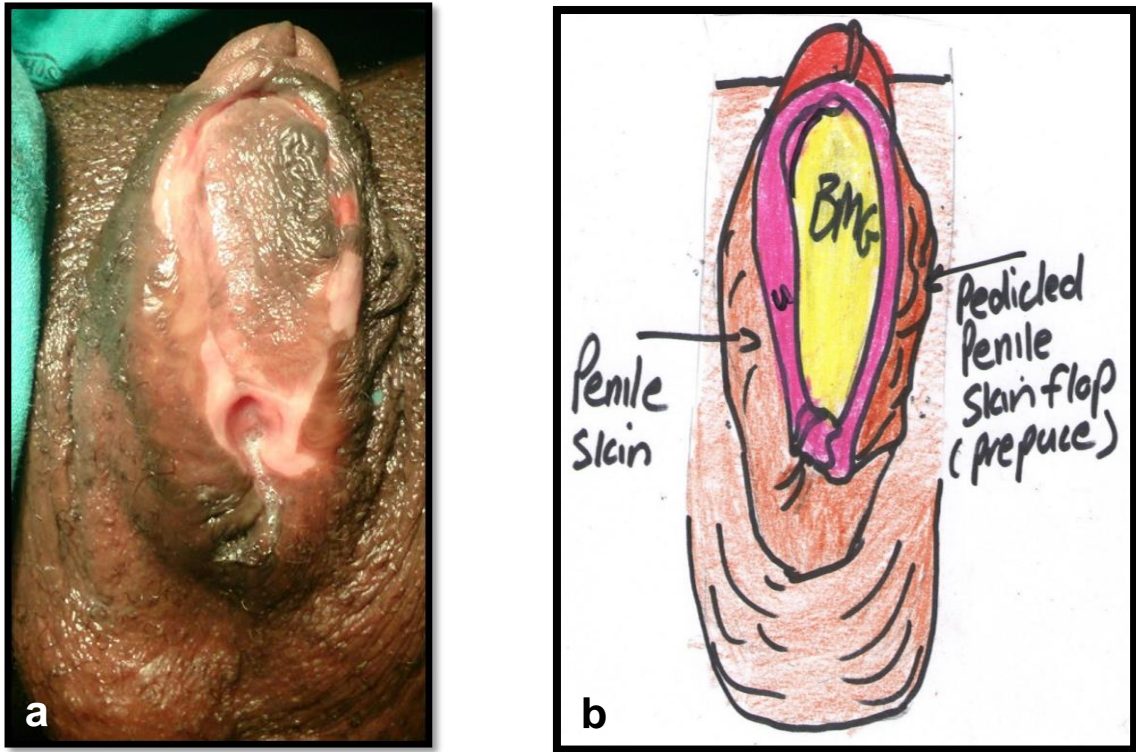
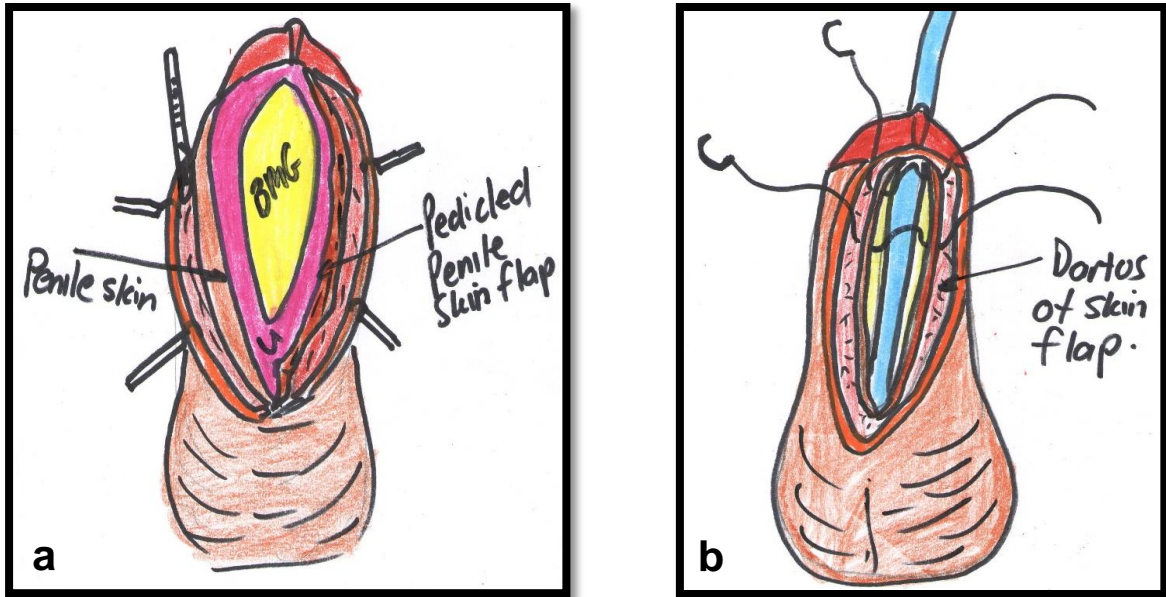


Figure 5.6. (a) Appearance of the first stage before the second stage is done. (b) Schematic drawing illustrating the anatomy.

After the first stage, catheters were left in for seven days. Thereafter patients urinated through a new opening that had been created behind the stricture. Second-stage reconstruction was done six months later after the tissue surrounding the urethra had healed and was soft and pliable. It is important to note that both ends of the distal and proximal urethra must be patent before performing the second stage, which is when the neo-urethra with vascularised pedicled penile skin flaps is closed.

The lateral penile skin flaps on the ventral sides of the bivalved urethra were mobilised and the neo-urethra created over a F16 silicone catheter with penile skin flaps closed in two layers with Vicral 4/0 (Figures 5.7 and 5.8). The transurethral catheter was removed three weeks post-procedure.



Figures 5.7. (a) Mobilisation of the pedicled penile skin flap and penile skin flaps. (b) Closure of the urethra with penile and pedicle penile skin flap over urethral catheter.

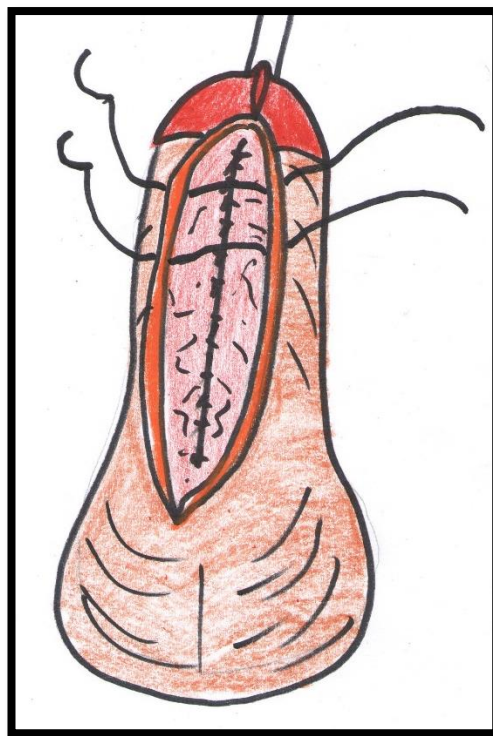


Figure 5.8. The skin is closed with interrupted 4/0 Vicryl sutures.

Results

The age of the seven patients ranged between thirty-seven and forty-five years (average forty-four years). Four patients presented with necrotising fasciitis secondary to peri-urethral abscess and they were debrided and a suprapubic catheter inserted before the first stage urethroplasty. None of the patients had had previous interventions in the form of dilatation, direct vision internal urethrotomy (DVIU) or urethroplasty to treat their urethral strictures. These patients had panurethral stricture disease and no lumen could be identified, thus requiring a two-stage procedure. The mean stricture length was 7.1 cm (range 6.1 cm to 10.2 cm). There were no complications reported after the first stage where there was good BMG take. The final success rate after the two-stage urethroplasty was 71 % (five out of seven) at twenty-four months' follow-up. The success was determined from the time when the catheter was removed after completion of the second stage. One patient presented with obstructive lower urinary tract symptoms and the RGU showed an anastomotic urethral stricture with diverticulum formation at the nine-month follow-up. This patient was treated with direct vision internal urethrotomy (DVIU) (Figure 5.1b). Another patient developed a urethracutaneous fistula at three weeks after the urethral catheter was removed. The cause of this urethracutaneous fistula was post-operative wound infection, which developed in the patient after the second stage urethroplasty. Two of the patients complained about post void dribbling and their urethragrams demonstrated small urethral diverticula. Regardless of this, they were satisfied with the results and did not desire any further treatment. In light of this, their treatment outcome was regarded as successful.

Discussion

The incidence of panurethral strictures secondary to inflammatory disease is unknown. In a retrospective study at a single centre, Palminteri *et al.* (2013) reported an incidence of 5% in patients with lichen sclerosis. Inflammatory urethral stricture disease secondary to sexual transmitted disease was the main cause in all seven patients described. Post-infective USD is a risk factor for urethroplasty failure in long segment urethral strictures but amendable with fasciocutaneous pedicled penile skin flaps (Mathur *et al.*, 2014). Panurethral strictures spanning the bulbar and penile urethra with obliterated urethral lumens are a surgical challenge when it is associated with adverse conditions, such as extensive perineum and scrotal skin scarring (Mathur *et al.*, 2014).

The majority of uncomplicated, non-inflammatory long anterior urethral strictures with non-obiterated lumens can be successfully managed with a single-stage procedure with an 89% success rate (Tabassi *et al.*, 2011). Penile skin flaps, which have ample vascular pedicle, were considered the most reliable material for reconstruction of long or complex strictures (McAninch *et al.*, 1998). Reported success rates of circular fasciocutaneous flaps, for single stage reconstruction, have reached a 79% success rate after ten years' follow-up (Whitson *et al.*, 2008). In cases where a tubularised preputial or penile skin flap is used for urethroplasty, panurethral strictures have a success rate of 60% after three years (Xue *et al.*, 2016). However, it has been reported that these one-stage circumferential penile skin flaps have lower success rates when compared to two-stage repairs using free grafts in patients with panurethral stricture disease.

Two-stage repairs are generally accepted in patients with inflammatory urethral strictures secondary to lichen sclerosis (Kulkarni *et al.*, 2009). Further indications for a two-stage urethroplasty are those patients who had previously undergone urethroplasty with significant scarring of the surrounding skin (Joseph *et al.*, 2001). Joseph *et al.* (2001), report a revision rate for their two-stage urethroplasty for refractory anterior urethral strictures as 20% at four-year follow-up. In light of this, it is vital to determine whether to use a one-stage or a two-stage technique when repairing complex strictures (McAninch *et al.*, 1998).

Conflicting reports make this quite problematic. For example, in 1999 Mundy reported that the resticture rate was twice to three times higher for the one-stage than the two-stage procedure (Mundy, 1995). From another study, it appears that the two-stage urethroplasty has higher revision rates than the one-stage procedure where Dubey *et al.* (2003), report a 28% revision rate for the two-stage and 12% revision rate for the one-stage urethroplasty in patients with balanitis xerotica obliterans. However, Greenwell *et al.* (1999), reported a lower resticture rate of 13% for two-stage urethroplasty compared to the 30% in patients with inflammatory urethral strictures secondary to lichen sclerosis.

This study proposes a two-stage technique where the fibrotic urethra is incorporated in the repair, instead of resecting it in inflammatory stricture affecting long segments. It is argued that the incorporation of the fibrotic urethra limits the size of ventral vascularised

penile flaps that are needed to close the ventral aspect of the urethra. Incorporating the fibrotic urethra theoretically ensures a healthy strong lateral side support to the neo-urethra, which may limit the risk of diverticulum formation. In theory it may also help to align the urethra, which will make it easier to perform a cystoscopy after urethroplasty.

The fasciocutaneous penile skin flap that was created during the first stage ensured the creation of a urethra with non-hair-bearing skin during the second stage. This was the reason for using these skin flaps to close the ventral aspect of the neo-urethra. The results are promising as five out of the seven patients were happy with the result after the twenty-four months' follow-up. Foreseen complications when vascularised penile or preputial skin is used are recurrent stricture, post void dribbling and diverticulum formation, which occurred in two of the seven patient (Dubey *et al.*, 2003). However, the symptoms were not bothersome for the patients, probably due to the vast improvement in their quality of life. In this two-stage technique the BMG was placed dorsally because of better blood supply from the corpora cavernosum and the penile skin flaps ventral because of poor blood supply and graft backing. Erickson *et al.* (2001), used a similar technique by combining dorsal buccal mucosa onlay with ventral fasciocutaneous flap. Their success rate was 79% (eleven out of fourteen patients). It can be concluded from this case series that the incorporation of the scarred fibrotic urethra as part of the stage technique did not compromise the outcome. Furthermore, it was easier to treat the recurrent urethral stricture with cystoscopy and internal urethrotomy due to the alignment of the neourethra in the one patient with anastomotic stricture recurrence.

Conclusion

Long segment inflammatory obliterative disease of the urethra remains a daunting challenge. The results of dorsal onlay buccal mucosa graft, combined with vascularised pedicled penile skin incorporating the fibrotic and scarred urethra were promising in this case series that exhibited a success rate of 71%. In addition, procedure related complications were minimal. In spite of the small sample size, these results are encouraging in the setting of obliterative urethral strictures secondary to infection. Although more patients are needed for conclusive outcomes, this two-stage repair where the fibrotic urethra was incorporated is recommended to treat inflammatory obliterative panurethral strictures.

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Chapter 6

ARTICLE 4

Outcome determinants in the management of inflammatory anterior urethral strictures: Long-term results from central South Africa

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Abstract

Objective: To determine the impact of stricture length, position and degree of obliterative urethral lumen on the surgical outcomes of corrective procedures for inflammatory anterior urethral strictures.

Methods: A retrospective analysis was done using the records of patients who presented with proven infective anterior urethral strictures at the University of the Free State between 2007 and 2010. All patients had a follow-up time of longer than forty-eight months. Outcomes were analysed firstly according to age, presenting symptoms, aetiology, location and length of the stricture. Thereafter the long-term outcomes were analysed according to surgical procedure. Finally, outcomes of surgical procedures were sub-analysed according to type of obstruction, aetiology, length and position.

Results: The median age of patients was forty-seven years (range 21 to 86 years). Procedures were successful in 163/326, that is (50%) of patients. Direct vision internal urethrotomy (DVIU) was successful in 29/75, that is (39%) of patients. DVIU followed by regular urethral dilatations was successful in 28/71, that is (39%) of patients. Anastomotic urethroplasty (AR) was successful in 59/99, that is (60%) of patients. Augmented anastomotic urethroplasty (AAR) was successful in 11/15, that is (73%) of patients. The dorsal buccal mucosa graft urethroplasty (DBMGU) was successful in 23/32, that is (72%) of patients, significantly higher than that of 2/9, that is (22%) of patients who underwent the ventral buccal mucosa graft urethroplasty (VBMGU; $p=0.017$; HR 3.4; 95% CI 1.287–9.399). The one-stage circular pedicled penile skin urethroplasty (cPFU) was successful in 1/12, that is (8%) of patients. Patients that underwent two-stage urethroplasty had a success rate of 5/7, that is (71%) of patients. A primary component analysis PCA on the 163 failed procedures showed that stricture length was the main contributor for failure (eigen value of 1.79; 45%).

Conclusions: More invasive surgical procedures are required in inflammatory strictures compared to non-inflammatory strictures. This might be due to the underestimation of stricture length by RGU. Sonographic and MRI studies should be included routinely in the evaluation of inflammatory strictures.

Key words: Urethral stricture, infective, stricture location, stricture length, obliterative urethral lumens.

Introduction

There is a paucity of published data addressing the outcomes of the surgical management of inflammatory urethral strictures secondary to infection, the main cause of stricture in the developing world (Heyns *et al.*, 2012, Beyer *et al.*, 2010) The aetiology of stricture in the developed world was analysed by Lumen *et al.*, (2009) and demonstrated that the

main contributing causes were instrumentation (32%), idiopathic (23%), urethral catheters (13%), trauma (3%) and infection (3%).

Limited literature is available on inflammatory urethral strictures secondary to gonococcal infection. In the studies available, authors identified several shortcomings. Firstly, analyses and comparison of outcomes data are complicated by the non-uniform nature of urethral strictures, which differ in length, location and aetiology (Eswara *et al.*, 2015). Secondly, studies do not distinguish between inflammatory and traumatic aetiology and finally, infective urethral strictures have been identified as a risk factor for urethroplasty failure (Mathur *et al.*, 2014). As the inflammatory process differs significantly from other causes of urethral obstruction and stricture, published surgical data on the selection and outcomes of procedures performed in a non-inflammatory setting might not be applicable in an inflammatory setting. This can explain the high failure rate in the management of inflammatory stricture (Mathur *et al.*, 2014). The aim of this study is to determine the outcomes of different surgical procedures in inflammatory urethral stricture in relation to stricture length, position and the degree of obliteration of the urethral lumen affected by analysing the success rates after the first interventions performed in central South Africa.

Methodology

A retrospective analytical cohort study of 326 consecutive patients who underwent surgical treatment for inflammatory urethral strictures between 2007 and 2010 was performed using hospital records. Patients with a history of purulent urethral discharge and microbial evidence of gonococcal infection were included as well as patients with purulent urethral discharge treated at a referring institution. Patients with a history of trauma, iatrogenic, catheter related strictures, and Lichen sclerosis, which usually occurs in the navicular fossa, were included, whilst patients with membranous strictures, which are almost exclusively traumatic or those of unknown aetiology, were excluded from this study. Patients were included in this study after a minimum of forty-eight months' follow-up period. The follow-up time in months was determined from the day of treatment to the last clinic follow-up date.

Outcomes of different surgical procedures for inflammatory urethral strictures were analysed in three categories. Firstly, in relation to the length of the stricture, secondly, in

relation to the position of the stricture and lastly, whether the stricture was obliterative or not. The length of the strictures was determined by retrograde and prograde urethrograms (RUG) in centimetres. Urethral sonography and MRI were not used routinely during the study period. The location of the lesions was documented as penile, peno-bulbar, bulbar and pan-urethral. Pan-urethral stricture disease was assigned if the patient had low grade strictures throughout the length of the penile and bulbar urethra. Lesions were classified as obliterative or non-obliterative, based on the pre-operative RUG. Functional success was assigned if the patient reported an improvement in voiding symptoms and urinary quality of life. When a patient presented with obstructive lower urinary tract symptoms suggestive of recurrence, a follow-up RUG was performed. Treatment failure was defined as recurrence of symptoms requiring re-investigations (RUG) or any intervention for stricture recurrence. Data were analysed to determine the role of the procedure type, length, position and obliterative urethral lumens on outcomes and surgical management of inflammatory urethral strictures.

Statistical analysis. The Kaplan-Meier estimator was used to estimate failure-specific stricture free rates. Stricture free rates were measured in months and were censored at the date when a patient developed stricture recurrence. The frequencies were subjected to a Chi-square test. Statistical significance was set at $p < 0.05$. The effect size was calculated using Cramer's V statistic. This test statistic is used to measure the strength of association between two nominal variables, and the values range between 0 and 1. Values close to 0 indicate a weak association between the variables and values close to 1 indicate a strong association between the variables. Analyses were done using SPSS release 15.0 (SPSS Inc. Chicago, IL, USA). A principal component analysis (PCA) was performed on the variables in the failed procedures to determine the variables that contributed the most to failure and included stricture length, position and presenting symptoms (R-software).

Results

Stricture characteristics and procedures:

A total of 326 patients with a median age of forty seven years (range 21 to 86 years) with infective urethral strictures underwent treatment for anterior urethral stricture between 2007 and 2010. The urethral strictures were located as follows: Penile urethra in 34 patients (10%), peno-bulbar urethra in 113 patients (35%) and bulbar urethra in 128

patients (39%). Patients presented with the following symptoms: Acute urinary retention secondary to obliterated urethral lumens in 211 patients (65%), obstructive lower urinary tract symptoms with non-obliterated lumens in 86 patients (26%) and perineum sepsis in 29 patients (9%). The median follow-up was sixty-three months (range 48 months to 70 months). The surgical outcomes per procedure are presented in Table 6.1. Note that the overall success rate was only 50% (163/326).

Table 6.1. Surgical outcomes analyses of 326 patients treated for inflammatory urethral stricture per procedure.

Procedure	Patient numbers (n)	Mean age Years	Success rate		Mean follow up time in months
			%	n	
DVIU	74	54.5 (30 -86)	39	29	59.2 (50 - 66)
DVIU + DIL	71	46.8 (22-84)	39	28	60.1 (50 – 65)
AR	99	45.9 (21 – 80)	60	59	59.5 (48 – 70)
AAR	15	43.2 (30 – 76)	73	11	58 (48 – 65)
DBMG	32	52.5 (21 – 82)	72	23	58.3 (48 – 65)
VBMG	9	47.8 (25 – 73)	22	2	59 (50 – 62)
cPFU	12	52.4 (35 – 72)	8	1	60 (48 – 66)
PU	5	46.2 (34 – 70)	80	4	62 (52 – 66)
Two – stage Urethroplasty	7	45.8 (34 – 68)	71	5	56 (48 – 58)

DVIU = direct vision internal urethrotomy, AR = anastomotic urethroplasty, AAR = anastomotic urethroplasty augmented with buccal mucosa, DBMGU = dorsal onlay buccal mucosa graft urethroplasty, VBMGU = ventral onlay buccal mucosa urethroplasty, cPFU = circular fasciocutaneous penile skin flap urethroplasty, PU = perineum urethrostomy.

The success rate of the dorsal buccal mucosa graft urethroplasty was 23/32 patients, (72%), which is significantly higher than that of 2/9 patients, (22%) who underwent the ventral buccal mucosa graft urethroplasty (VBMGU; $p=0.017$; HR 3.4; 95% CI 1.287–9.399). The one-stage circular pedicled penile skin urethroplasty (cPFU) was successful in 1/12 patients (8%). Patients that underwent two-stage urethroplasty had a success rate of 5/7 (71%).

Procedures and length groups: The results are summarised in Table 6.2. For strictures less than 2 cm in length, both DVIU and DVIU with serial dilatations had long-term successful outcomes of only 39%. In contrast AR, ARR and DBMGU had success rates

in excess of 65%. For stricture lengths that were between 2.1 cm to 4.0 cm, the most successful outcomes were achieved with DBMGU (81%) and AAR (75%; Table 6.2). The two-stage urethroplasty where BMG was combined with ventral pedicled penile skin flap achieved a 71% success rate for strictures longer than 4 cm (Table 6.1).

Table 6.2. The outcome of procedures for specific length groups. The perineum urethrostomies and Johanson procedures were excluded from analysis.

Procedure	Mean length in cm (median)	Length groups in centimetre	Patient number (n)	Success rate %	n	p-value	Confidence interval for the effect size w
DVIU	1.0 (0.3 - 7.0)	to 2.0 2.1 to 4.0	62 4	39 0	24 0	0.1233	w=0.1188 95% CI: 0.00 - 0.4333
DVIU+DIL	1.2 (0.2 - 7.0)	to 2.0 2.1 to 4.0	51 13	39 31	20 4	0.5744	w=0.070 95% CI: 0.00 - 0.3129
AR	1.3 (0.3 - 7.0)	to 2.0 2.1 to 4.0	82 14	65 43	53 6	0.1218	w=0.158 95% CI: 0.00 - 0.3580
AAR	3.1 (1.0 - 6.0)	to 2.0 2.1 to 4.0	4 8	100 75	4 6	0.2733	w=0.316 95% CI: 0.00 - 0.8819
DBMGU	4.6 (0.6 - 10.0)	0.1 to 2.0 2.1 to 4.0	7 16	71 81	5 13	0.599	w=0.110 95% CI: 0.00 - 0.5133
VBMGU	3.5 (1.0 - 4.5)	0.1 to 2.0 2.1 to 4.0	2 6	50 17	1 1	0.3458	w=0.333 95% CI: 0.00 - 1.026
cPFU	5.0 (3.7 - 7.0)	0.1 to 2.0 2.1 to 4.0	0 4	0 0	0 0	Not estimable	Not estimable
Two - stage Urethroplasty	8.0 (4.0 - 9.0)	0.1 to 2.0 2.1 to 4.0	0 1	0 100	0 1		Sample size too small

*The DVIU and DVIU +Dilatations were done for low grade non obliterative urethral strictures. DVIU = direct vision internal urethrotomy, AR = anastomotic urethroplasty, AAR = anastomotic urethroplasty augmented with buccal mucosa, DBMGU = dorsal on-lay buccal mucosa graft urethroplasty, VBMGU = ventral on-lay buccal mucosa urethroplasty, cPFU = circular fasciocutaneous penile skin flap urethroplasty, PU = perineum urethrostomy.

Stricture location: It is noteworthy that DVIU had a success rate of only 22% in the bulbar region. DVIU as well as DVIU with dilatation did not achieve a success rate over 50% in any location (Table 6.3).

AR and ARR were successful in the peno-bulbar area with success rates of more than 66%. AAR was successful in 71% and 80% in the peno-bulbar and bulbar regions, respectively. DBMGU achieved a success rate of 77% in the penile location, with favourable outcomes in the peno-bulbar (67%) and bulbar regions (80%). Patients with pan-urethral strictures were excluded from Table 6.3.

Table 6.3. The success rates of procedures in the different stricture locations.

Procedure	Stricture position	Patients	Success rate n	Success rate %	p-value for position	Confidence interval for the effect size w
DVIU	Penile	6	3	50	0.178	w=0.256
	Pen-bulbar	20	10	50		95% CI:
	Bulbar	27	6	22		0.00 - 0.4422
DVIU+ DIL	Penile	9	1	11	0.150	w=0.274
	Pen-bulbar	25	10	40		95% CI:
	Bulbar	32	16	50		0.00 - 0.4663
AR	Penile	1	0	0	0.400	w=0.141
	Peno-bulbar	38	25	66		95% CI:
	Bulbar	53	34	64		0.00 - 0.3193
AAR	Penile	2	2	100	0.308	w=0.490
	Peno-bulbar	7	5	71		95% CI:
	Bulbar	5	4	80		0.00 - 0.8940
DBMGU	Penile	13	10	77	0.811	w=0.173
	Peno-bulbar	12	8	67		95% CI:
	Bulbar	5	4	80		0.00 - 0.3910
VBMGU	Penile	1	1	100	0.076	w=0.756
	Peno-bulbar	3	1	33		95% CI:
	Bulbar	5	0	0		0.00 - 16.500
cPFU	Penile	2	1	50	0.141	w=0.674
	Peno-bulbar	8	0	0		95% CI:
	Bulbar	1	0	0		0.00 - 1.144

DVIU = direct vision internal urethrotomy, AR = anastomotic urethroplasty, AAR = anastomotic urethroplasty augmented with buccal mucosa, DBMGU = dorsal on-lay buccal mucosa graft urethroplasty, VBMGU = ventral on-lay buccal mucosa urethroplasty, cPFU = circular fasciocutaneous penile skin flap urethroplasty, PU = perineum urethroplasty.

Outcomes by obliterative vs. non completely obliterative lumens: The results are summarised in Table 6.4. The DVIU success rate was only 27% in twenty-five patients with obliterative urethral lumens, significantly lower than the 54% success rate in forty-one patients with non obliterative lumens ($p=0.005$). Obliterative urethral lumens had no negative impact on the success rates of DVIU combined with dilatations, AR and AAR (Table 6.2). AR, AAR and DBMGU had success rates of 73%, 73% and 72% respectively, in patients with obliterative lumens. The two-stage urethroplasty BMG combined with pedicled penile skin flap had higher success rate when compared to the one-stage cPFU in patients with obliterative lumens, 71% vs. 8% ($p = 0.010$).

Table 6.4. Procedure success rates in obliterative and non-obliterative lumens and perineum sepsis.

Procedure (number of patients)	Non obliterative lumens success rate		Obliterative lumens success rate		Perineum sepsis success rate		p-value	Confidence interval for the effect size w
	%	(n)	%	(n)	%	(n)		
DVIU (74)	54	41	27	25	0	8	0.005	w=0.369 95% CI: 0.1073 - 0.5821
DVIU+DIL (71)	40	25	39	46	NA	NA	NA	NA
AR (99)	47	17	64	78	25	4	0.153	w=0.195 95% CI: 0.00 - 13.7625
AAR (15)	50	2	73	11	50	2	0.525	w=0.213 95% CI: 0.00 - 5.7618
Substitution urethroplasty								
DBMGU (32)	100	1	67	27	100	4	0.314	w=0.269 95% CI: 0.00 - 10.591
VBMGU (9)	NA	NA	22	9	NA	NA	NA	
cPFU (12)	NA	NA	10	1	2	0	0.640	w=0.250 95% CI: 0.00 - 5.7618
Two-stage urethroplasty (7)	NA	NA	100	1	67	6	NA	

NA = not analysed or not applicable, DVIU = direct vision internal urethrotomy, AR = anastomotic urethroplasty, AAR = anastomotic urethroplasty augmented with buccal mucosa, DBMGU = dorsal on-lay buccal mucosa graft urethroplasty, VBMGU = ventral on-lay buccal mucosa urethroplasty, cPFU = circular fasciocutaneous penile skin flap urethroplasty, PU = perineum urethrostomy.

Primary component analysis was performed on the 163 patients who had failed procedures to determine which of the variables (stricture length, position and presenting symptoms) contributed significantly to the failed outcome. The stricture length of the 163 patients who had failed the first procedures, contributed 45% to the variance of the data and the stricture position 27%. The eigen values of these two variables were above 1, indicating that these variables were the primary components causing failure. Stricture

length, but not stricture position was the main contributor in failed urethroplasty: AR (49%), DBMGU (74%), VBMGU (59%) and the one-stage cPFU (62%).

Discussion

In this study the long-term outcomes of surgical interventions of inflammatory strictures were evaluated. An attempt was made to relate outcomes of the specific procedure to the length and location of the stricture. The impact of whether the stricture was obliterative or not, was also considered.

In this study the overall success rate for endoscopic and urethroplasty procedures was 50%. This can be attributed to the post infective inflammatory process and underestimation of stricture length with RGU (Mathur *et al.*, 2014). RGU as the only imaging modality underestimates urethral stricture length (El-Ghar *et al.*, 2010). In the patients with infective urethral strictures, urethral ultrasound in adjunct with RGU determine the stricture length more accurately and preoperative ultrasonography has been recommended to accurately assess the extent of spongiosclerosis in an effort to decrease the recurrence rate (Barbagli *et al.*, 2003, Choudhary *et al.*, 2004). However, due to anatomical limitations, ultrasound it is not recommended as the sole assessment tool for strictures and should be combined with urethrography (Barbagli *et al.*, 2003). The use of ultrasonography changes the surgical approach in 19% of patients in a retrospective study that compared ultrasonography and RGU (Barbagli *et al.*, 2003). The best results in this series were obtained when stricture repair was augmented with a dorsal onlay buccal mucosa graft in both AAR and DBMGU. These procedures possibly compensated for the incorrect diagnosis of stricture length (Table 6.1).

Stricture length remained the main determinant of the success of procedures. In AR, studies showed no difference in outcome for lengths shorter and/or longer than two centimetres in predominantly non-inflammatory strictures (Elthaway *et al.*, 2007). Elthaway *et al.* (2007) report 99% success rate in 260 patients with mainly trauma and catheter related urethral strictures, which had a mean length of 1.9 cm located in the bulbar urethra. Trauma related bulbar strictures of 2 cm is the ideal length to treat with AR and high success rates were reported (Santucci *et al.*, 2002). However, Morey *et al.*, (2006) report a 91% success rate in eleven patients with bulbar urethral strictures

between 2.6 cm to 5.0 cm who underwent AR. Although AR is reserved for stricture lengths shorter than 2cm, Aghaji *et al.* (2001) reported a success rate of 88% in their group of ninety-eight patients where the length was 3 cm. In the inflammatory strictures reported in this study a much lower success rate of only 65% with AR was obtained in patients with bulbar strictures shorter than two centimetres and a very low success rate of 43% for strictures between 2 cm and 4 cm (Table 6.2). AR also had a significantly better outcome in strictures shorter than 2 cm, compared to strictures longer than 2 cm. It therefore appears from this study that in inflammatory urethral strictures AR should only be considered for shorter stricture lengths and definitely in cases of less than 2cm.

The AAR technique, which combines the anastomotic urethroplasty with substitution graft has been suggested for bulbar strictures between 2 cm to 4 cm (Guralnick *et al.*, 2001). Hoy *et al.* (2013) reported a 96.9 % patency rate achieved with a dorsal on-lay augmented anastomotic urethroplasty for a mean stricture length of up to 4.6 cm. In this study AAR achieved a success rate of 73% in fifteen patients, which is markedly lower than the 90% reported by the literature (Abouassaly *et al.*, 2007). An interesting finding was that AR had a lower success rate (65%) when compared to AAR (100%) or to that of the DBMGU (71%), even for stricture lengths between 0.1 to 2.0 cm (Table 6.2). This once again raises the question of underestimation of stricture length and suggests that AAR and DBMGU procedures compensate for that.

The preferred approach by many institutions for bulbar strictures longer than 4 cm, is circumferential urethral reconstruction with a patch or vascularised flap. Whitson *et al.* (2008) reported a ten-year stricture recurrence free rate of 79% in patients who underwent circular pedicled penile skin flap urethroplasty. However, contradictory results were found in inflammatory strictures in central South Africa where circular pedicled penile skin flap urethroplasty had an overall success rate of only 8%, much lower than the success rates (72%) of DBMGU and the two-stage urethroplasty (71%) (Table 6.1).

Strictures longer than 4 cm were identified as an important risk factor for failure and the preferred approach is a circumferential repair with skin flaps or grafts (Mathur *et al.*, 2014, Carney *et al.*, 2002). The best results for strictures longer than 4 cm were obtained with the DBMGU (56%) and the two stage urethroplasty (80%) (Table 6.2).

In this study infective strictures were located mainly in the bulbar and peno-bulbar urethra, contradictory to the penile urethra reported in the literature (Fenton *et al.*, 2005). Stricture location has an effect on stricture length, where penile strictures tend to have longer mean stricture lengths compared to that of bulbar strictures, mean of 6.1 cm vs. 3.1 cm (Fenton *et al.*, 2005). This study showed that stricture location did not affect the treatment outcome. However, penile strictures require more complex procedures due to the thinner spongiosum in the penile urethra compare to the bulbar urethra (Eswara *et al.*, 2015). In the patients who underwent urethroplasty, the stricture location had no negative affect on the treatment outcome (Table 6.3). This is in contrast to Breyer *et al.* (2010), who stated that strictures located in the penile urethra has a higher recurrence rate after repair.

A complete obliterative urethral lumen had a negative influence only when DVIU was used (Table 6.4). This finding was confirmed by one of the few prospective studies, which showed that the percentage urethral narrowing predicts the success rate of DVIU (Fenton *et al.*, 2005). DVIU is less time consuming and is therefore ideally suited to treat short urethral strictures when theatre time is limited (Heyns *et al.*, 1998). DVIU and DVIU followed by urethral dilatations were done in patients who had obliterative urethral lumens instead of urethroplasty, due to the lack of theatre time available. The 30% to 40% curative success rate of DVIU is consistent with the findings of this study (Lauritzen *et al.*, 2009). Repeat urethral dilatations after DVIU was of no value and had the same success rate as DVIU in this study. When patients do self-intermittent urethral dilatations after DVIU it inevitably only delay stricture recurrence but did not improve the success rate (Heyns *et al.* (1998). Obliterative urethral lumens had no negative influence on the success rates for AR, AAR and dorsal BMG urethroplasties (Table 6.4). In summary, obliterative urethral lumens played no role in the complexity of urethral strictures when urethroplasty was done, mainly because the obliterative lumens were excised or augmented to a favourable calibre. This is one of the reasons why obliterative urethral lumens were excluded from the urethral score validation (Eswara *et al.*, 2015).

Suggestions for management

The suggested management is based on stricture length and position, as determined by the RGU. Ultrasonography as an adjunct diagnostic modality with the RGU may alter this recommendation and now forms part of our standard pre-operative evaluation protocol.

DVIU can be used for urethral strictures shorter than 1 cm.

Urethral dilatations after DVIU is not recommended as it did not improve the success rate of DVIU alone.

AR is recommended for bulbar urethral strictures of ± 1 cm and definitely shorter than 2 cm.

AAR is the recommended approach for strictures shorter than 2 cm located in the bulbar urethra. Substitution urethroplasty with BMG is recommended and the placement of graft must be dorsal for strictures 2 cm to 4 cm in length.

In pan-urethral strictures or stricture lengths longer than 4 cm, a two-stage urethroplasty is recommended instead of substitution urethroplasty with buccal mucosal graft or circular fasciocutaneous flap urethroplasty.

Limitations

The retrospective nature of this study and the fact that the procedures were done by different surgeons made data interpretation difficult. The selection of procedures was biased because it was done by different surgeons with different skill levels.

Conclusion

Underestimation of inflammatory urethral stricture length was the biggest single contributor towards failed procedures. In general, more invasive procedures yielded better results in inflammatory strictures compared to published outcomes of procedures in non-inflammatory lesions. Therefore, DVIU should only be considered in very short 0.5 cm to 1 cm lesions, AR for lesions less than 1 cm to 2 cm, AAR in 1 cm to 3 cm and DBMGU in lesions 2 cm to 4 cm in length. The two-stage urethroplasty is the preferable approach to treat patients with stricture lengths > than 4 cm. Location, and to lesser extent symptoms, played minor roles in failures. In patients with infective urethral strictures the placement of the BMG may determine the success of substitution urethroplasty. The BMG must be placed dorsal instead of ventral. Obliterative urethral

lumens had no negative effect on the success rates of urethroplasty in patients with infective strictures.

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Chapter 7

CONCLUSION

Inflammatory urethral stricture is a common and debilitating disease in South Africa and the developing world. High incidences of sexually transmitted diseases (STD's) and specifically gonococcal disease, result in strictures which are not only longer in length but also has twice the long-term failure rate compared to other causes of urethral strictures (Statistics South Africa Quarterly Labour Force Survey, Quarter 1, 2016). Published data, specifically addressing the management of inflammatory urethral strictures remain in short supply.

In order to develop a rational approach to inflammatory urethral strictures, the anatomy, inflammatory processes and the pathophysiology of urethral strictures, standard surgical procedures and expected outcomes were described in the literature review.

In addition, two retrospective studies were conducted and the use of two modified surgical procedures were described (Chapters 3 and 6). These results were used to develop a treatment algorithm for inflammatory urethral strictures (*vide infra*).

The incidence of gonococcal related urethral strictures was 81% in patients treated for urethral stricture disease at the Universitas Academic Hospital. Literature relating to infective urethral strictures is sparse and mainly reports on iatrogenic or catheter related strictures. The literature furthermore indicates that the success rate of any type of procedure used in the treatment of urethral stricture disease deteriorates over a period of ten years.

7.1) The long-term outcome of direct vision internal urethrotomy (DVIU) and urethroplasty in patients treated for anterior urethral stricture disease in central South Africa: A seven-year follow-up.

The treatment failure was higher in infective urethral strictures than that of trauma-related strictures. The significant decrease in stricture-free survival in the first eighteen months is noteworthy and could possibly have contributed to the infective nature of the strictures and an ongoing inflammatory process. The role of re-infection should also be determined.

It is imperative that stricture length be determined by routine sonography and also possibly MRI in order to accurately determine the length of the obstruction. Stricture location had no negative effect on the treatment outcome. AR could be performed safely for stricture lengths of 1.5 cm and shorter. An indication for the use of AAR is a stricture length of up to 3 cm. Dorsal placement of the BMG, rather than ventral placement had significantly better outcomes in a small group of patients. Circular PFU had a poor long-term outcome in this study and a two-stage procedure should probably be considered in similar centres (Chapter 3).

7.2) Outcome determinants in the management of anterior urethral strictures: the central South African experience.

Stricture length proved to be the biggest contributor to failed procedures when the data of all the failed procedures were analysed. Location, and to a lesser extent symptom, played minor roles in failures. It was demonstrated that, in patients with infective urethral strictures, the BMG must be placed dorsal instead of ventral. Obliterative urethral lumens had no negative affect on the success rates of urethroplasty in patients with infective strictures. The two-stage urethroplasty is the preferred approach to treat patients with panurethral strictures (Chapter 6).

7.3) Anastomotic urethroplasty with double layer continuous running suture re-anastomosis versus interrupted suture re-anastomosis for infective bulbar urethral strictures: A prospective randomised trial.

Anastomotic urethroplasty performing a watertight double layer re-anastomosis with early catheter removal had a cure rate comparable to the conventional interrupted suture anastomosis with fourteen day catheterisation. Although the sample size was small, the catheterisation removal on day one after anastomotic urethroplasty appears to have played no role in the outcome of anastomotic urethroplasty in Group 1. The presence of minimal extravasation cleared up without negatively influencing the success rate. Therefore, small amounts of contrast extravasation do not warrant reinsertion of the catheter as long as the patient has a patent urethra. In conclusion, the double layer continuous running suture re-anastomosis made early discharge and urethral catheter removal possible and is not associated with an increase in re-stricture formation in the short to medium term. This technique warrants further study with larger patient numbers and extended follow-up periods in patients with bulbar strictures of up to 2.5 cm (Chapter 4).

7.4) A modified two-stage urethroplasty technique for inflammatory pan-urethral stricture management.

Long segment inflammatory obliterative disease of the urethra remains a daunting challenge. The results of dorsal onlay buccal mucosa graft combined with vascularised pedicled penile skin incorporating the fibrotic and scarred urethra were promising in this case series, in which the success rate was 71%. In addition, procedure related complications were minimal. Regardless of the small sample size, these results are encouraging in the setting of obliterative urethral strictures secondary to infection. Although more patients are needed for conclusive outcomes, this two-stage repair, where the fibrotic urethra was incorporated is recommended to treat inflammatory obliterative pan-urethral strictures. (Chapter 5).

In summary

Infective urethral strictures were significantly longer than trauma related urethral strictures. Infective urethral strictures had a mean length of 2.2 cm and the trauma related urethral strictures a mean of 1.5 cm. The overall success rate of first procedures in patients with infective urethral strictures, (43%) versus those with traumatic urethral strictures (72%), was significantly different. Patients with infective urethral strictures had a 2.6 times higher re-stricture rate compared to trauma related strictures at any given time during follow-up. Infectious strictures were mainly located in the bulbar (39%) and peno-bulbar areas (37%). With results of only in 10% of cases, the penile urethra was the least affected. Treatment failure was defined as the need for any procedure to treat the stricture after the initial first procedure.

Stricture length was the main determining factor for the success of procedures and the principle contributor towards failure in patients with infective urethral strictures. As a result, the treatment algorithm for strictures located in the bulbar and penile urethra was based on length (Figures 7.1 and 7.2). Figure 7.1 illustrates the treatment of infective urethral strictures located in the penile urethra and Figure 7.2 illustrates urethral strictures located in the bulbar urethra. The stricture length was determined with retrograde and/or prograde urethragrams, which was the only imaging modality available at the UAHC. Although RGU has limitations, ultrasonography or MRI urethrography was not available at the Universitas Academic Hospital Complex and the proposed treatment algorithm lengths were based on the RGU findings.

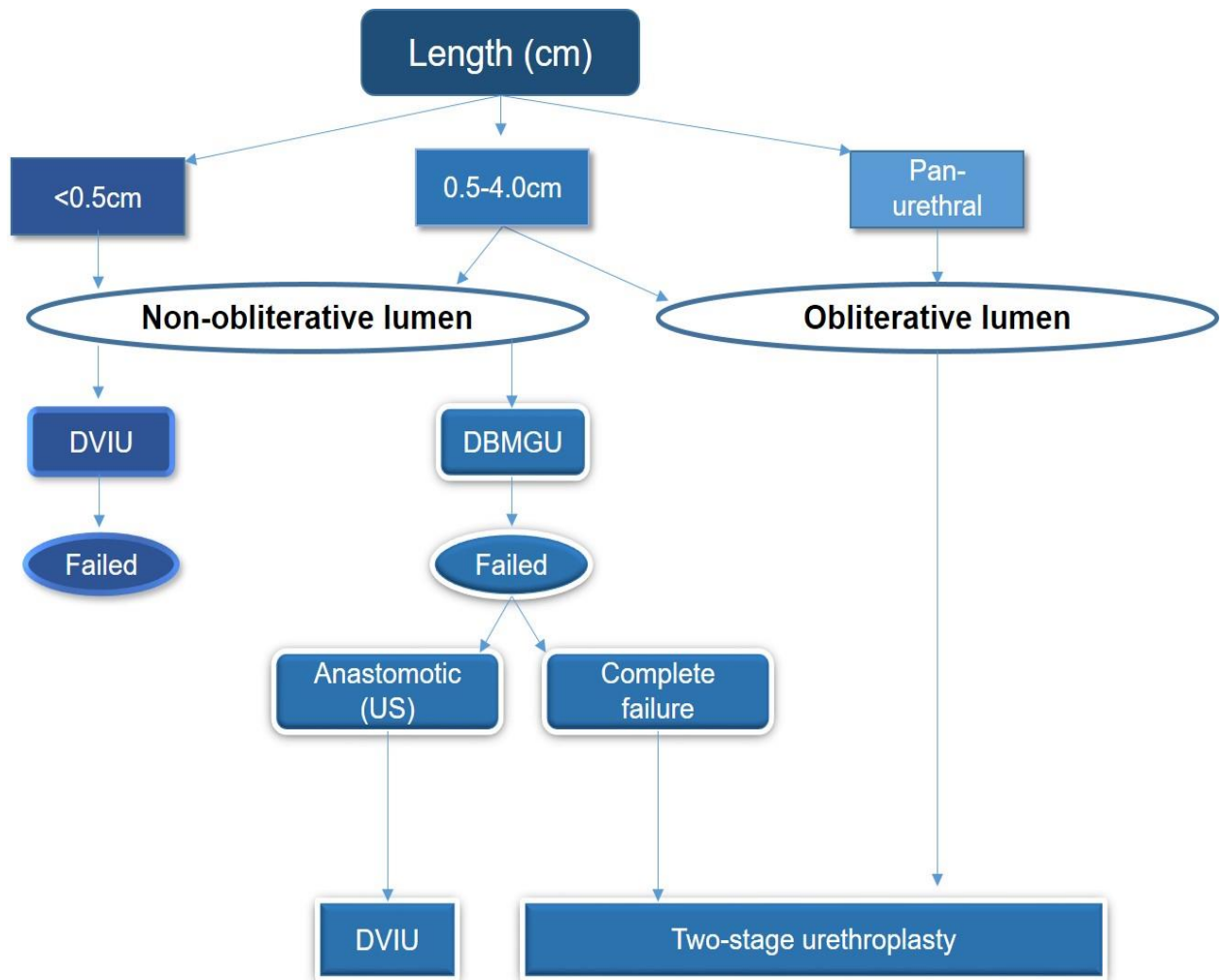


Figure 7.1. Treatment algorithm for infective penile urethral strictures. DVIU: Direct vision internal urethrotomy, DBMGU: Dorsal buccal mucosa graft only urethroplasty and US: urethral stricture.

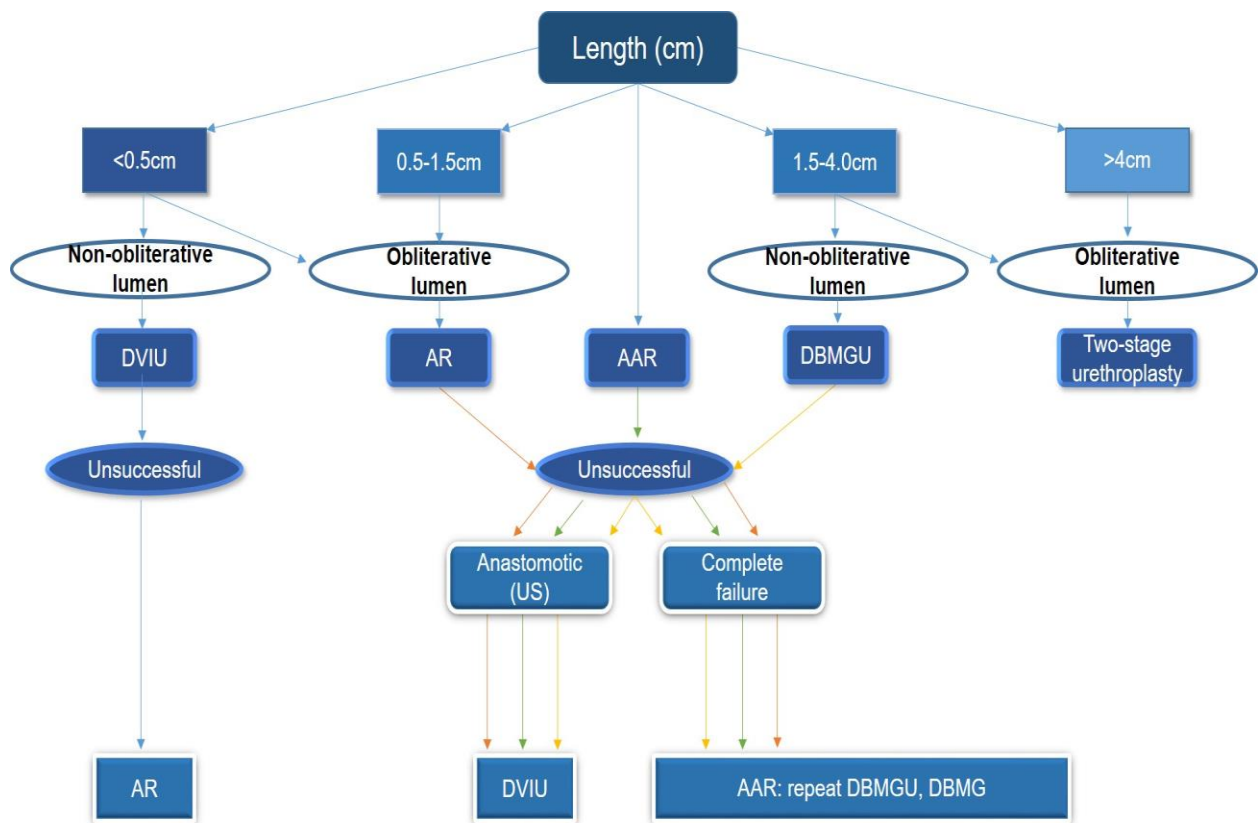


Figure 7.2. Treatment algorithm for infective bulbar and bulbo-penile urethral strictures. DVIU: Direct vision internal urethrotomy, DBMGU: Dorsal buccal mucosa graft onlay urethroplasty and US: urethral stricture.

Obliterative urethral lumens did not negatively affect the success rates of urethroplasty. The inclusion of obliterative urethral lumens in the algorithm was purely technical. It is easier to do a DBMGU where the urethral lumen is not obliterated. Obliterative urethral lumens influenced the success rates of DVIU and not the success rates of urethroplasty procedures (Chapter 6).

Stricture location, be it penile or bulbar, did not play a marked role in failure of any of the urethroplasty procedures (Chapter 3 and 6). The treatment algorithm distinguishes between penile and bulbar urethral strictures due to the fact that, for example, AR is technically easier to perform for bulbar strictures and is not indicated for penile strictures.

The long-term success rates of procedures were much lower when compared to that reported in the literature. This can be attributed to the infective nature of the stricture and

the limitations of RGU diagnosing the correct length, which can accurately demonstrate the stricture location but not the exact length of the stricture.

AR is a relatively easy procedure to treat bulbar urethral strictures. The literature reports success rates of up to 99%. The results showed a much lower success rate of 59% with AR when it was done with interrupted sutures in patients with a median stricture length of 1.5 cm. To improve this, a length of 1.5 cm is recommended for anastomotic urethroplasty, instead of the recommended 2 cm. The shorter length will compensate for the inability of the RGU to accurately diagnose the correct length. This is the reason for recommending a length of 1.5 cm in the algorithm (Figure 7.2).

AR failed in those patients with a median length of 1.5 cm and contradictory to the literature, a 90% success rate was reported in patients with the same mean length (Chapter 3).

The poor results achieved with AR prompted the modification of the AR technique. After excision of the stricture the anastomosis was done with a double layer continuous running suture and not with interrupted sutures. The benefit of this modification was that the urethral catheter could be removed within twenty-four hours and so limited the risk of pressure necrosis by the urethral catheter. In a randomised trial, this modification resulted in a success rate of 90% compared to the 71% achieved with the conventional AR with interrupted sutures (Chapter 4). The double layer continuous running suture re-anastomosis after stricture excision showed promising results. It is possible that this technique ensures better blood supply for subsequent healing (Chapter 4).

AAR with a success rate of 73% was superior to the success rate of 59% of AR (Chapter 3). It is possible that AAR compensates for the underestimation of stricture length when RGU is used to determine the length. Histological analysis clearly demonstrated that the length was underestimated due to the presence of fibrosis in the two normal appearing urethral ends that were anastomosed after excision of the stricture (Chapter 2). AAR was the preferred procedure for bulbar strictures longer than 2.0 cm, where a 73% success rate was achieved in infective urethral strictures with mean lengths of 2.6 cm (Chapter 3).

Placement, be it dorsal, ventral or lateral of the BMG is a contentious issue when performing substitution urethroplasty. This research indicated that the ventral placement of the BMG had poor results with only 22% being stricture free after five years. The dorsal placement of the BMG had a significantly higher success rate of 72% compared to the ventral placement (Chapters 3 and 6). The VBMGU had a 3.4 times faster re-stricture rate when compared to the DBMGU. It is likely due to the fact that placement of BMG dorsally, ensures good blood supply from the corpora cavernosum for improved graft take and healing. The poor results from the ventrally placed BMG is likely due to the fact that the urethral spongiosum is fibrotic with poor blood supply, which may have a negative effect on graft healing. Histologically, the peri-luminal area of the urethra is affected in infective strictures and not the luminal epithelium, which appears normal (Chapter 2). Fibrosis of the sub-epithelial area is mainly responsible for the luminal narrowing and this is where the BMG graft is placed with a ventral onlay.

It is generally accepted that stricture lengths of 4 cm and longer are a risk factor for failure. Results in this research suggest that lengths of 3 cm and longer are a risk factor. The overall success rates for all procedures combined were significantly lower for stricture lengths of 3 cm and longer, compared to those shorter than 3 cm (Chapter 3). The recommended approach for stricture lengths of 4 cm and longer is circumferential reconstruction with a patch or vascularised flap. The results showed that the one-stage circular PFU had a poor long-term success rate of only 8%. As a result, the modified two-stage repair was developed. This modification combines a dorsal BMG onlay with a ventral pedicled penile skin flap and incorporates the fibrotic urethra in the repair. The results look promising because the five-year patency rate was 71% (Chapter 5).

There was a sharp decrease in the overall stricture-free rates in the first eighteen months after treatment. This can be attributed to the infective nature of the urethral strictures. One of the debatable issues is, whether a flap or graft is the best to use when performing substitution urethroplasty to prevent the sharp decrease. An interesting find was that the DBMGU had better stricture free rates than the circular PFU. It appears that a BMG is superior to flaps in terms of success rates and slower stricture deterioration when used in substitution urethroplasty (Chapter 3).

DVIU is a relatively easy procedure to perform but the long-term results are dismal. The seven-year success rate of DVIU was 28% in patients with infective, traumatic, iatrogenic and unknown aetiology (Chapter 3). Attempts were made to increase the DVIU success rates by combining it with urethral dilatations. Other institutions found that urethral dilatations did not improve the success rate of DVIU but only increased the time to restricture. However, the results strongly suggest that urethral dilatations may be beneficial to patients with infective, traumatic, iatrogenic and unknown aetiology, where the overall success rate of DVIU improved from 28% to 43% (Chapter 3). However, in patients with infective urethral strictures, urethral dilatations were of no additional value because the success rates remained 39% (Chapter 6). The question of the influence DVIU may have on subsequent success rates of urethroplasty procedures however remained. The results of this study showed that DVIU had no negative affect on the success rate because it was 94% with AR in patients with failed DVIU (Chapter 3). For this reason, DVIU was included in the treatment algorithm. In the treatment algorithm DVIU is reserved for urethral strictures shorter than 0.7 cm, based on the findings of the first retrospective study (Chapter 3).

In summary, the results clearly indicate that stricture length was the most important predictor of the success of treatment in many cases, irrespective of the position of the stricture. It also led to algorithms that take length into account to improve success. In the algorithm different procedures are recommended for the different lengths, so as to improve success.

Recommendations for the treatment of infective urethral stricture disease

Ultrasonography as an adjunct investigation to RGU must be utilised so that the length of a stricture can be accurately determined.

AR is recommended for strictures shorter than 1.5 cm in the bulbar urethra when RUG is used as the only approach to determine the stricture length.

The double layer continuous running suture re-anastomosis after stricture excision is recommended, rather than the interrupted suture re-anastomosis when AR is done for bulbar urethral strictures.

AAR is recommended for urethral strictures longer than 1.5 cm in patients with infective urethral strictures located in the bulbar and penobulbar urethra.

The dorsal placement of the BMG, rather than ventral placement is recommended when substitution urethroplasty is done in patients with infective strictures in the bulbar and penile urethra.

The modified two-stage urethroplasty, where the fibrotic urethra is incorporated with the repair for pan-urethral strictures is recommended, rather than the one-stage circular pedicled penile skin urethroplasty.

Adjunctive urethral dilatations after DVIU is not recommended in patients with infective urethral strictures.

It is recommended that follow-up should exceed eighty-four months in order to determine the actual success rates of procedures.

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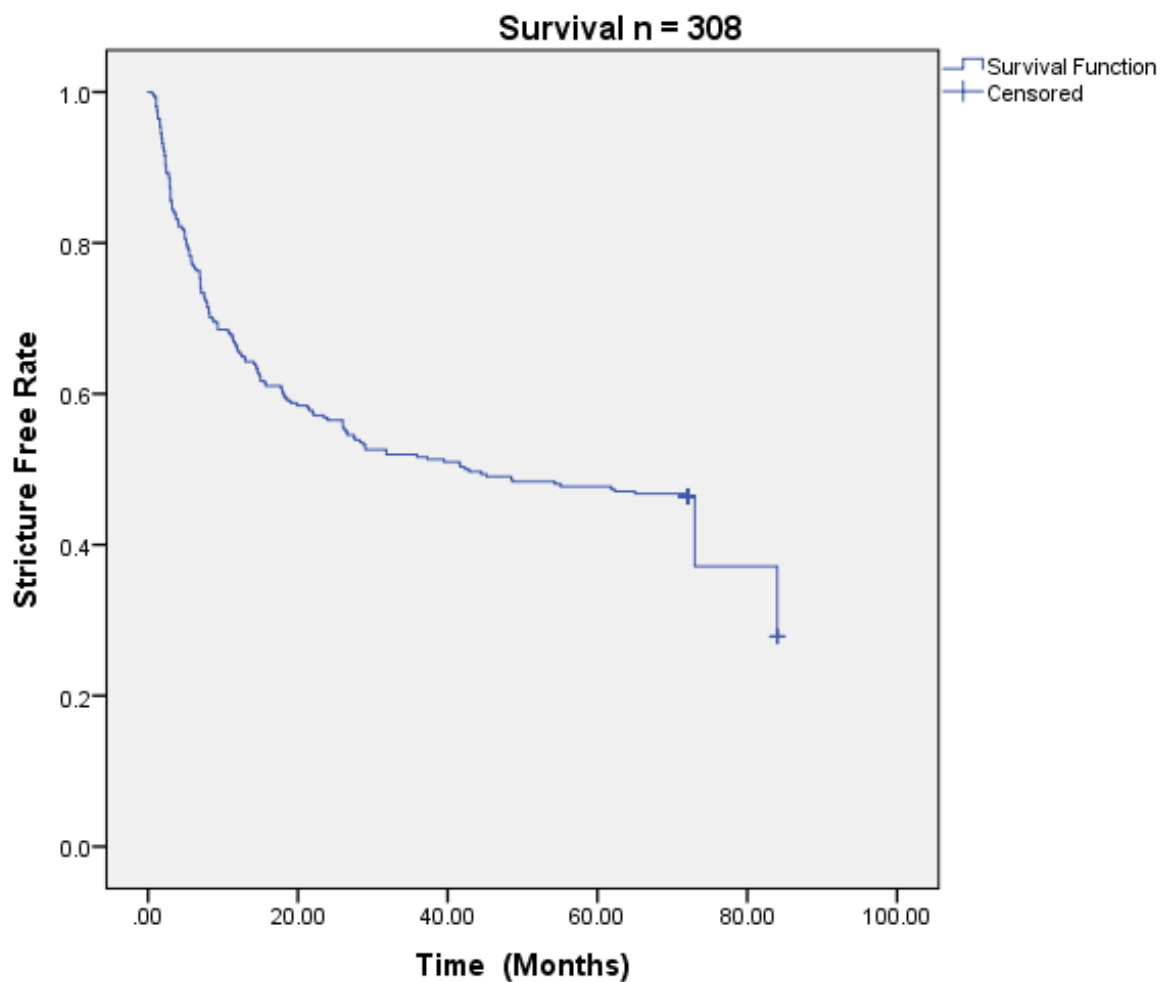
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APPENDICES

Appendix A

Chapter 1:

Statistical figures used for data interpretation but could not be included in articles because the figure and table numbers are limited.



Time in months	6	12	18	24	42	72	84
Success rate (%)	77	66	60	57	50	47	28

Fig. 1. Overall stricture-free rates of the 308 patients after 84 months follow-up.

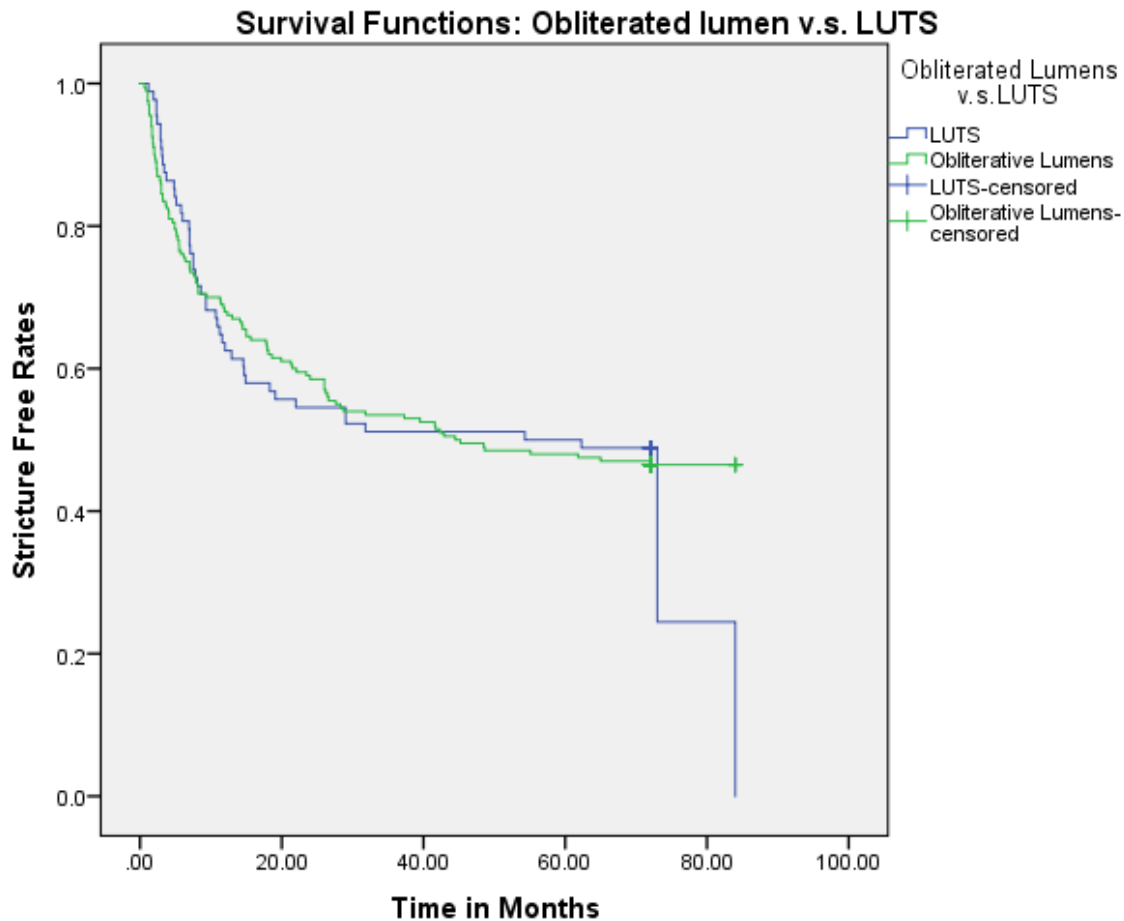


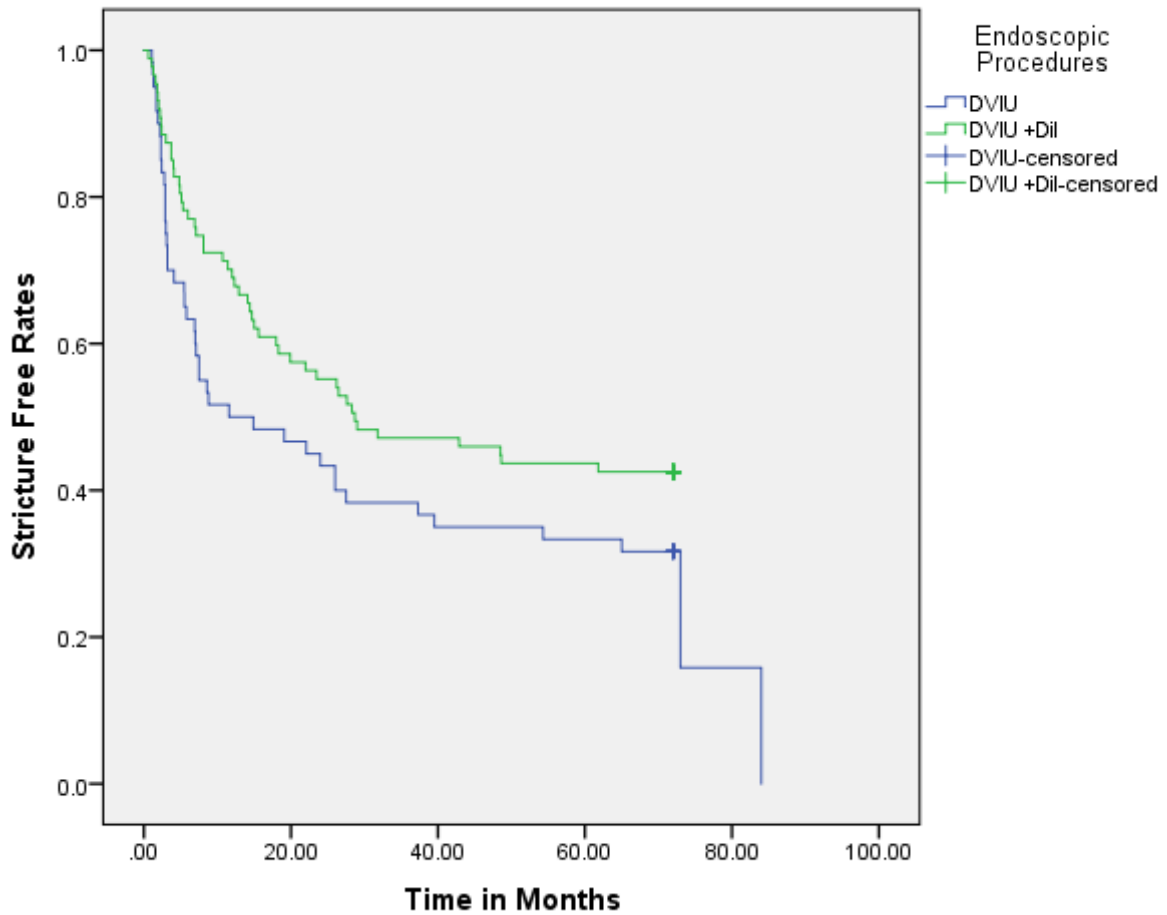
Figure 2. The overall stricture-free rates in patients with obliterated lumens and those who present with LUTS ($p=0.942$; 95% CI 41.375 – 50.419).

Table 1. Success rate of second procedures performed after failed first procedures.

Failed first procedure	Number patients	Overall success rate of second procedures
		n (%)
DVIU	42	34 (81.0)
DVIU + DIL	29	23 (79.3)
AR	33	27 (81.8)
AAR	2	1 (50.0)
Dorsal BMGU	4	2 (50.0)
Ventral BMGU	4	3 (75.0)
cPFU	12	7 (58.3)
Total	126	97 (77.0)

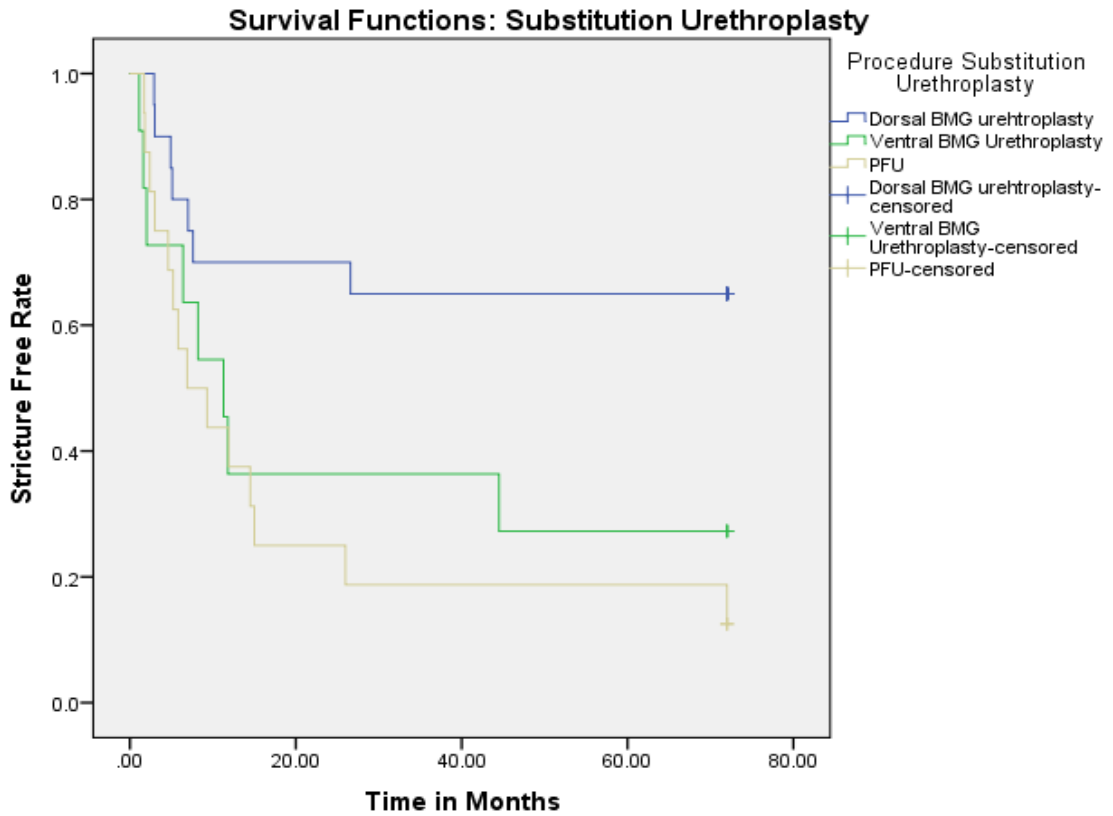
AAR = augmented anastomotic urethroplasty, AR = anastomotic urethroplasty; BMGU = buccal mucosa graft urethroplasty, cPFU = circular penile flap urethroplasty; DIL = dilatation, DVIU = direct vision internal urethrotomy.

Survival Functions: DVIU compared with DVIU combined with Dilatations



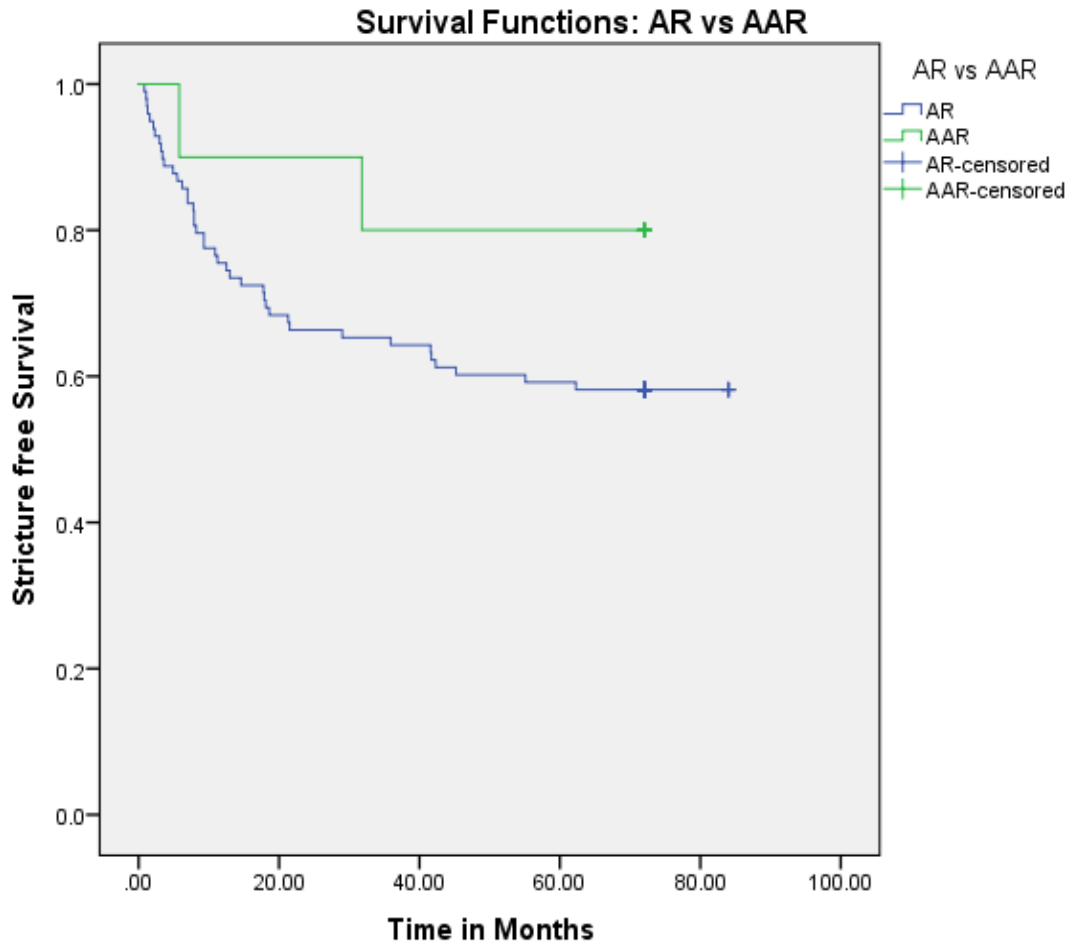
Time in months	6	12	18	24	27	39	65	73
Success rate %								
DVIU	62	50	47	43	38	35	32	16
DVIU + dilatation	77	69	60	55	52	45	43	43

Figure 3. Stricture-free survival rates of DVIU compared with DVIU combined with urethral dilatations (Breslow's generalised Wilcoxon; $p=0.059$).



Time in Months	6	12	24	p-value
Success rate (%)				
Dorsal BMG only	80	70	65	0.009
Ventral BMG only	64	36	36	
PFU	56	38	18	

Figure 4. The stricture-free rates for AAR and substitution urethroplasty.



Time in Months	6	12	18	36	60
Success rate					
AR	86	75	69	64	58
AAR	90	80	80	80	80

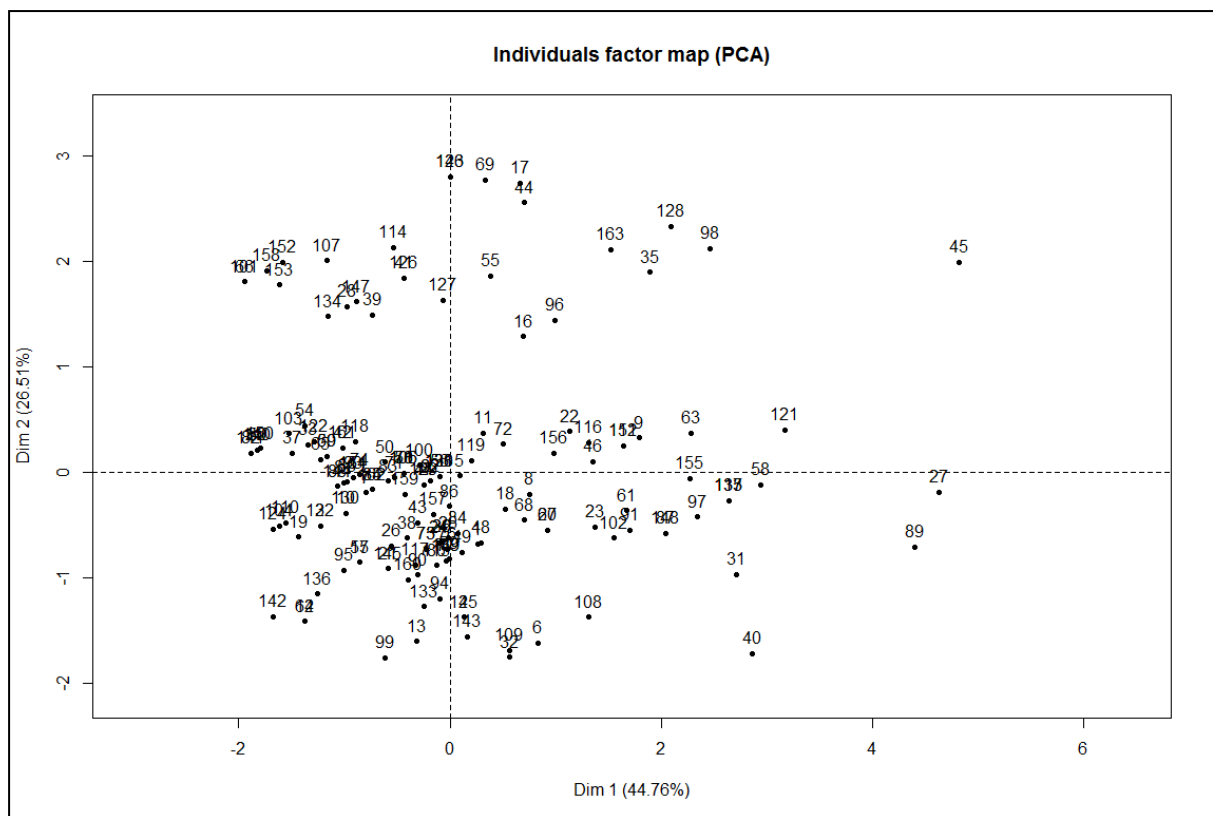
Figure 5. The stricture free rates for AAR compared to AR (Log rank $p=0.202$).

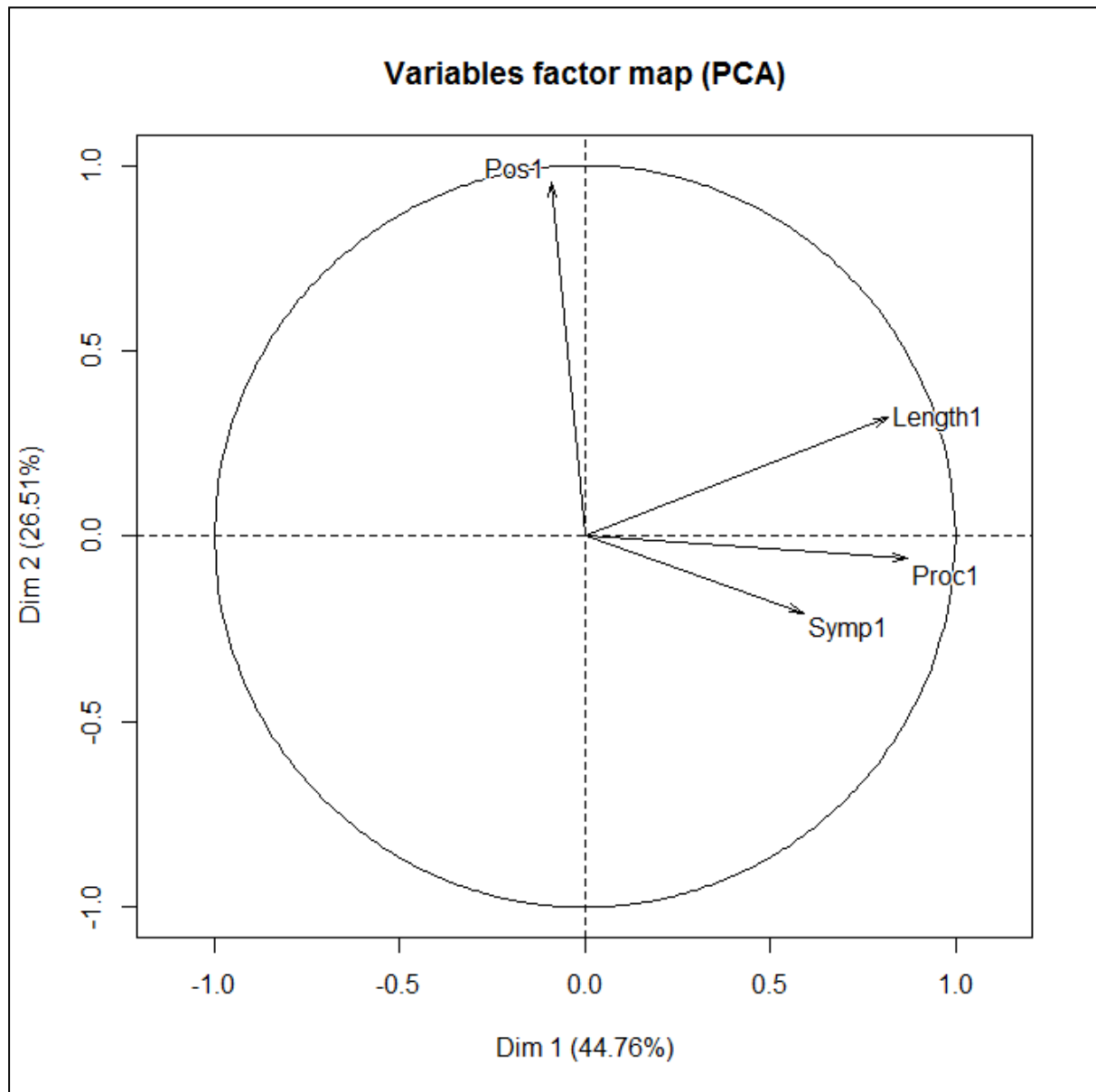
APPENDIX B

A primary component analysis

All procedures

	Eigenvalue	Percentage of variance	Cumulative percentage of variance
Stricture length	1.7905171	44.762928	44.76293
Stricture position	1.0604784	26.511960	71.27489
Presenting symptom	0.7969881	19.924703	91.19959
First procedure	0.3520164	8.800409	100.00000



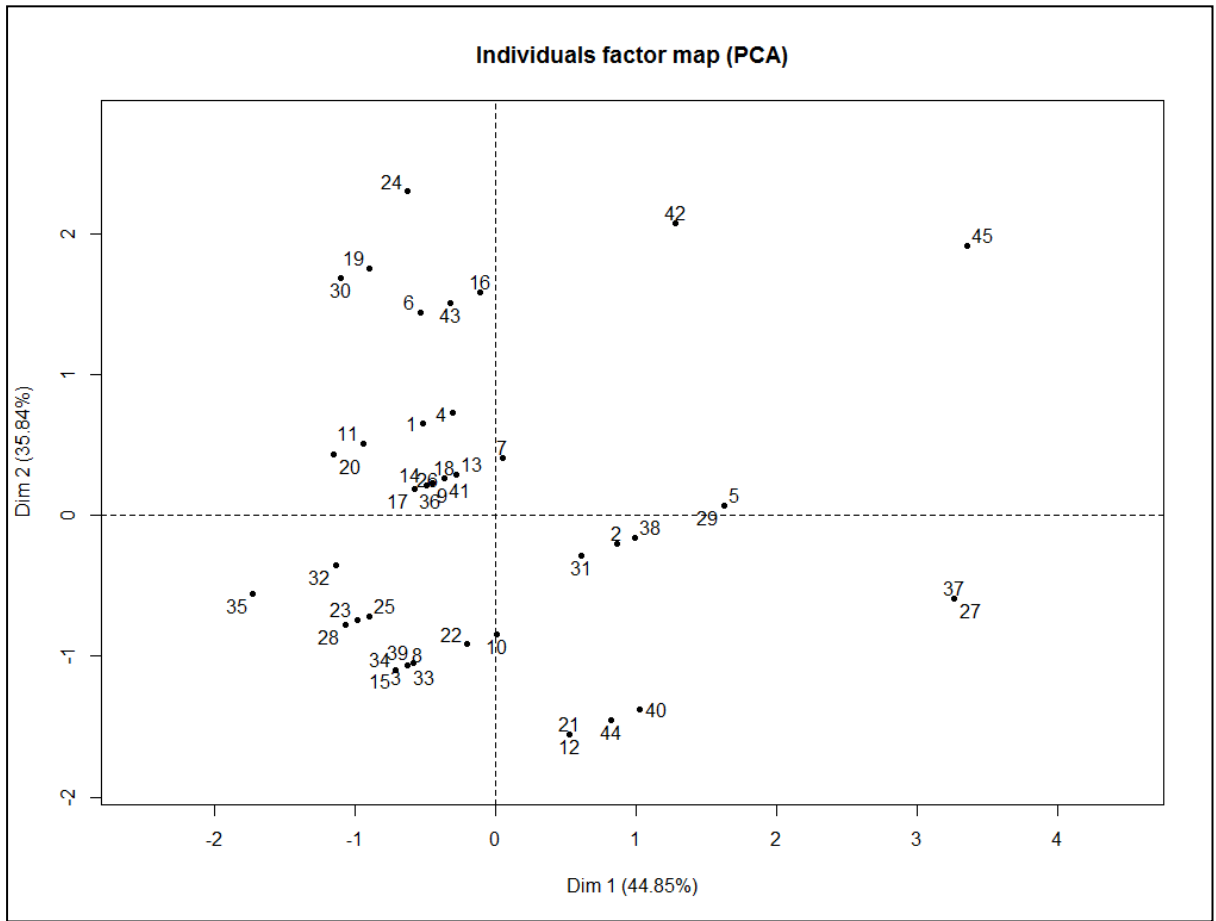


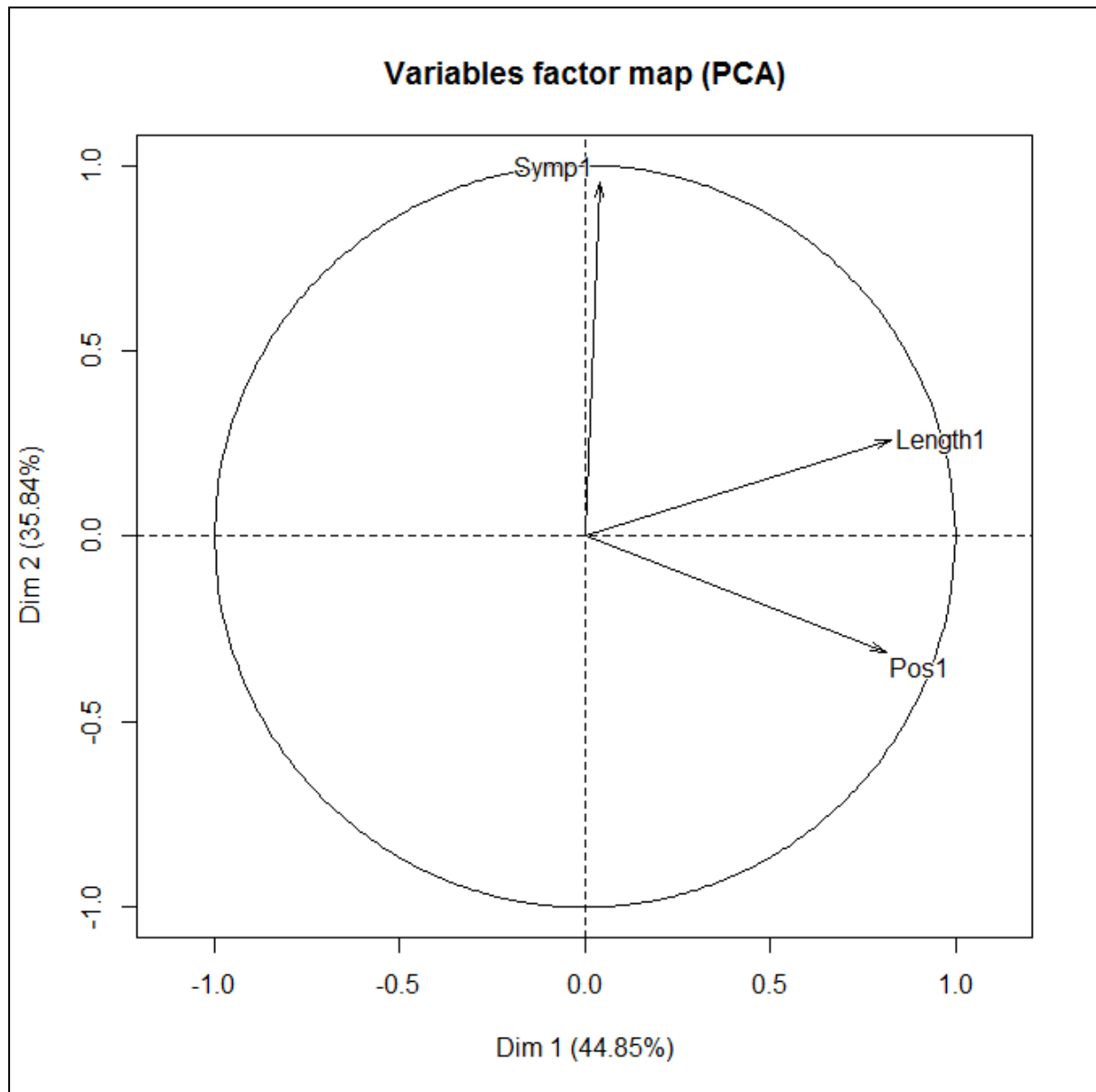
1. Procedure 1

No reported data.

2. Procedure 2

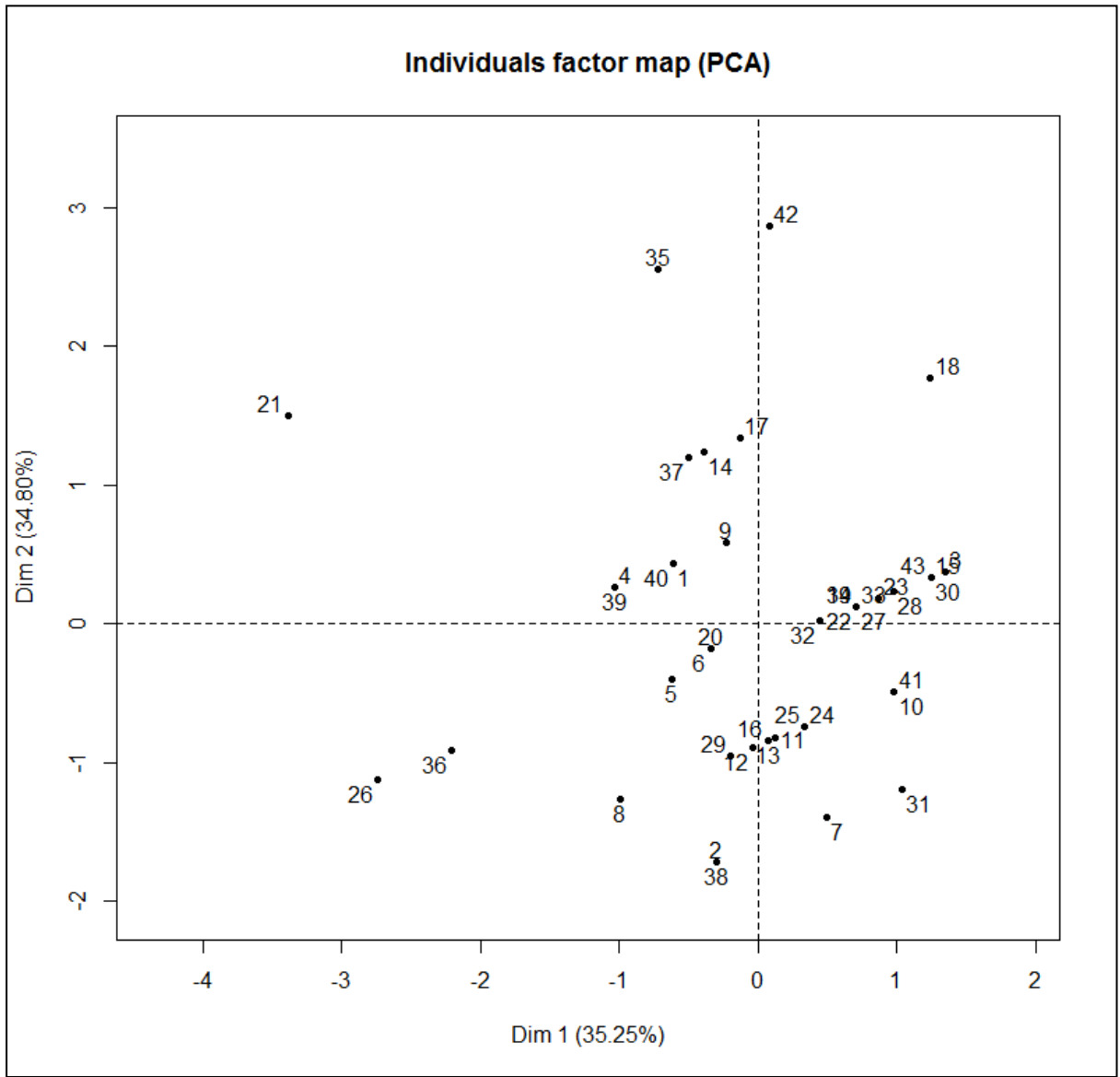
	Eigenvalue	Percentage of variance	Cumulative percentage of variance
Stricture length	1.3453780	44.84593	44.84593
Stricture position	1.0750777	35.83592	80.68186
Presenting symptom	0.5795443	19.31814	100.00000

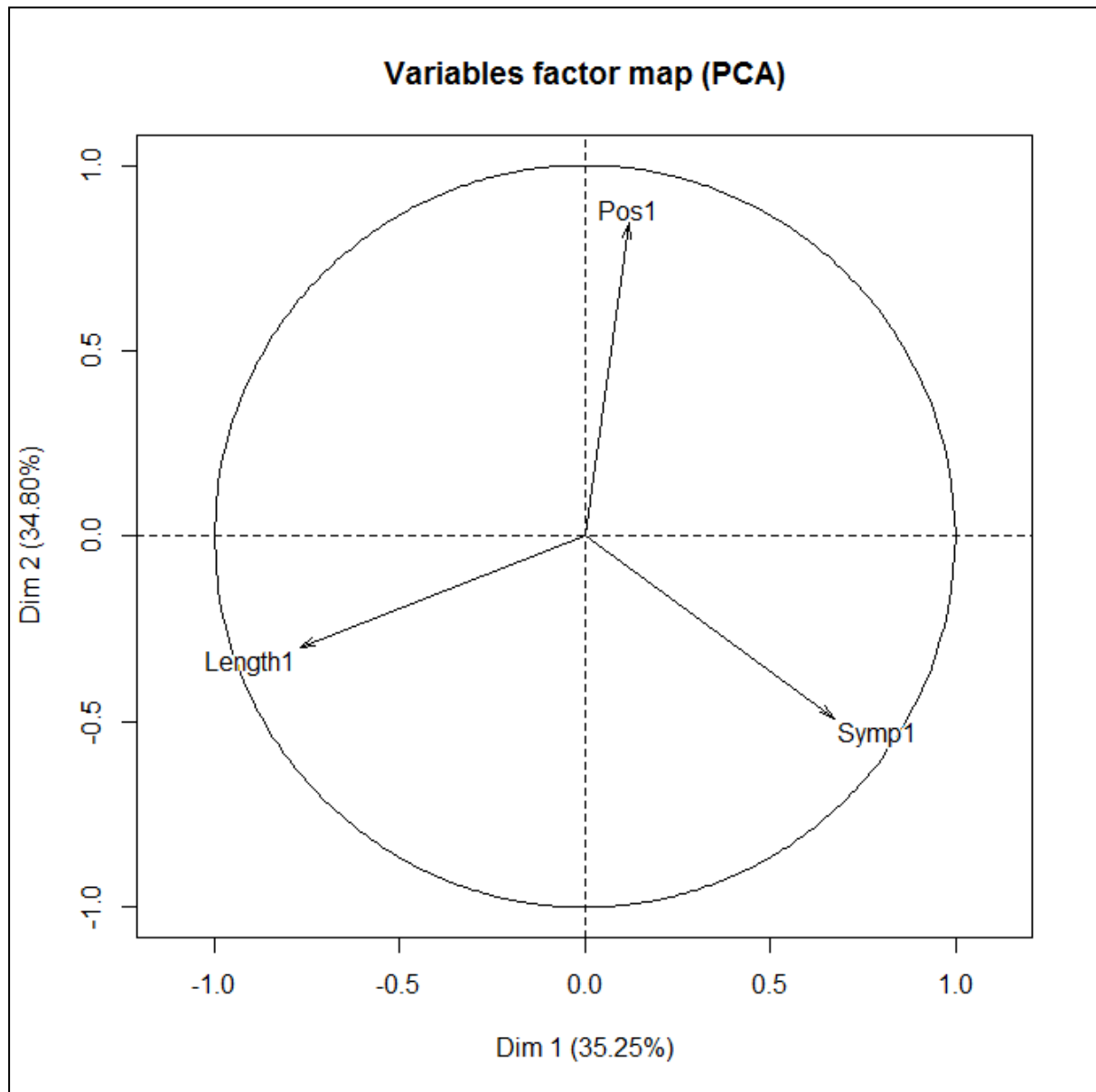




3. Procedure 3

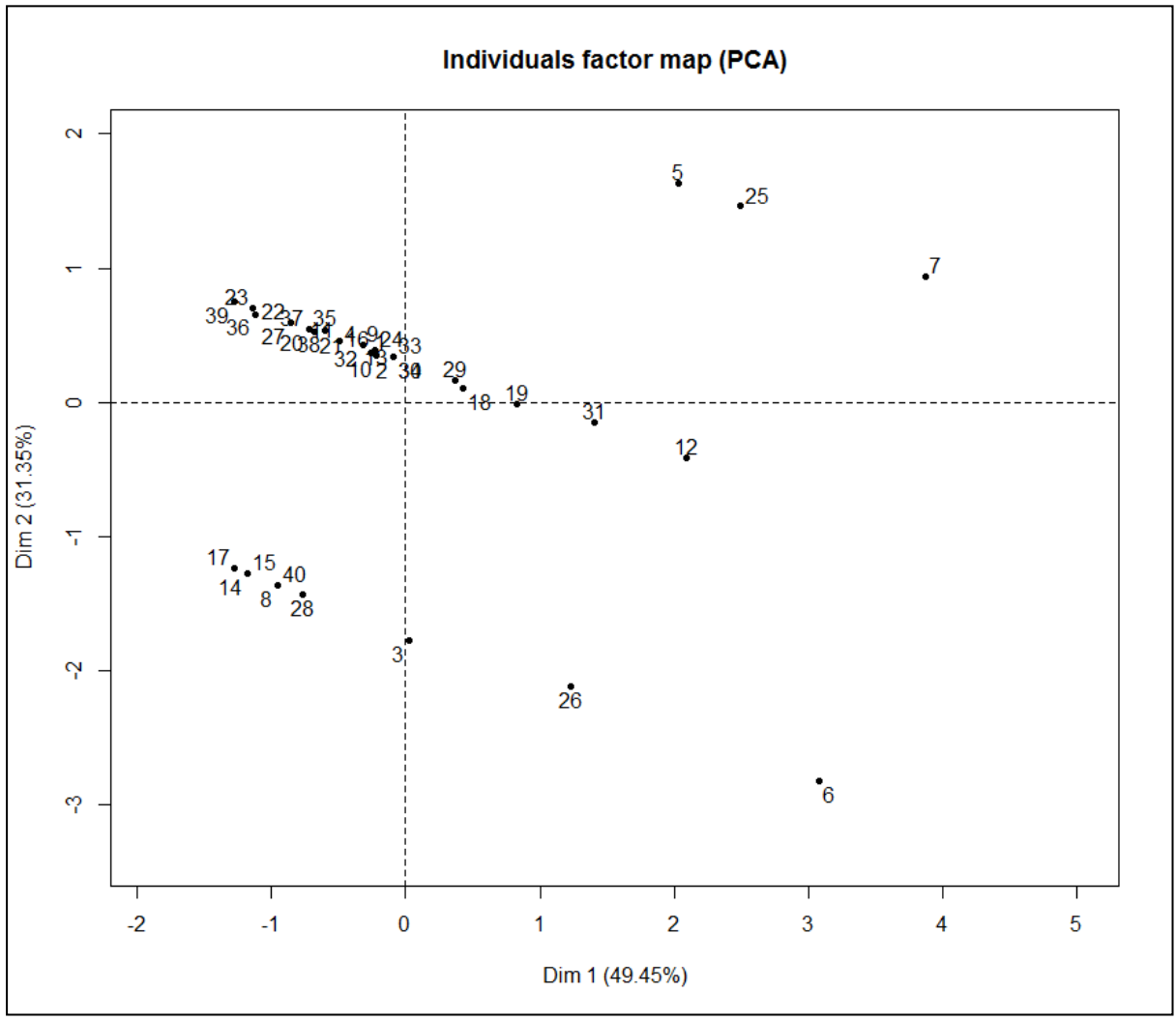
	Eigenvalue	Percentage of variance	Cumulative percentage of variance
Stricture length	1.0575731	35.25244	35.25244
Stricture position	1.0441088	34.80363	70.05606
Presenting symptom	0.8983182	29.94394	100.00000

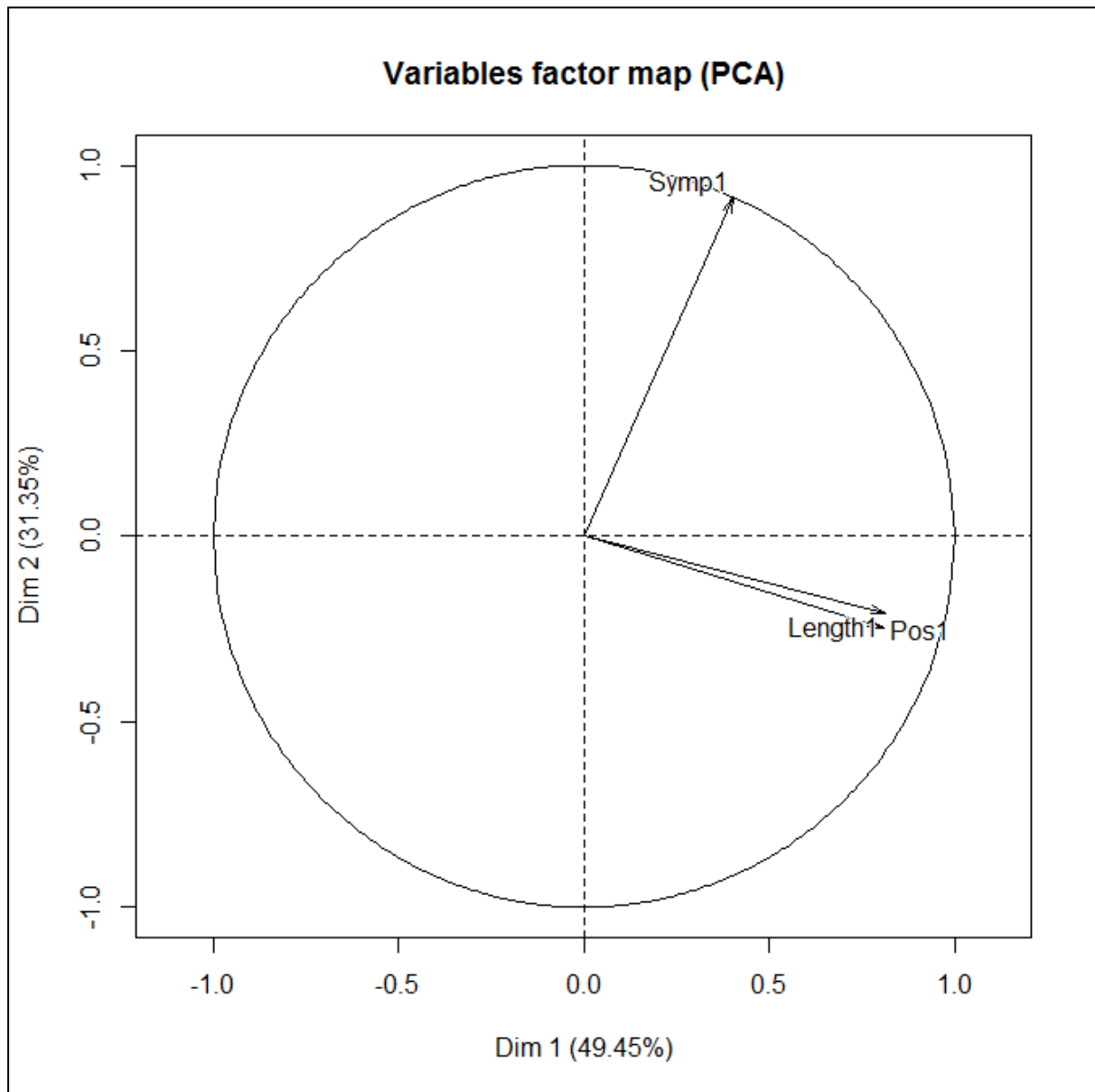




4. Procedure 4

	Eigenvalue	Percentage of variance	Cumulative percentage of variance
Stricture length	1.4833563	49.44521	49.44521
Stricture position	0.9406042	31.35347	80.79868
Presenting symptom	0.5760395	19.20132	100.00000



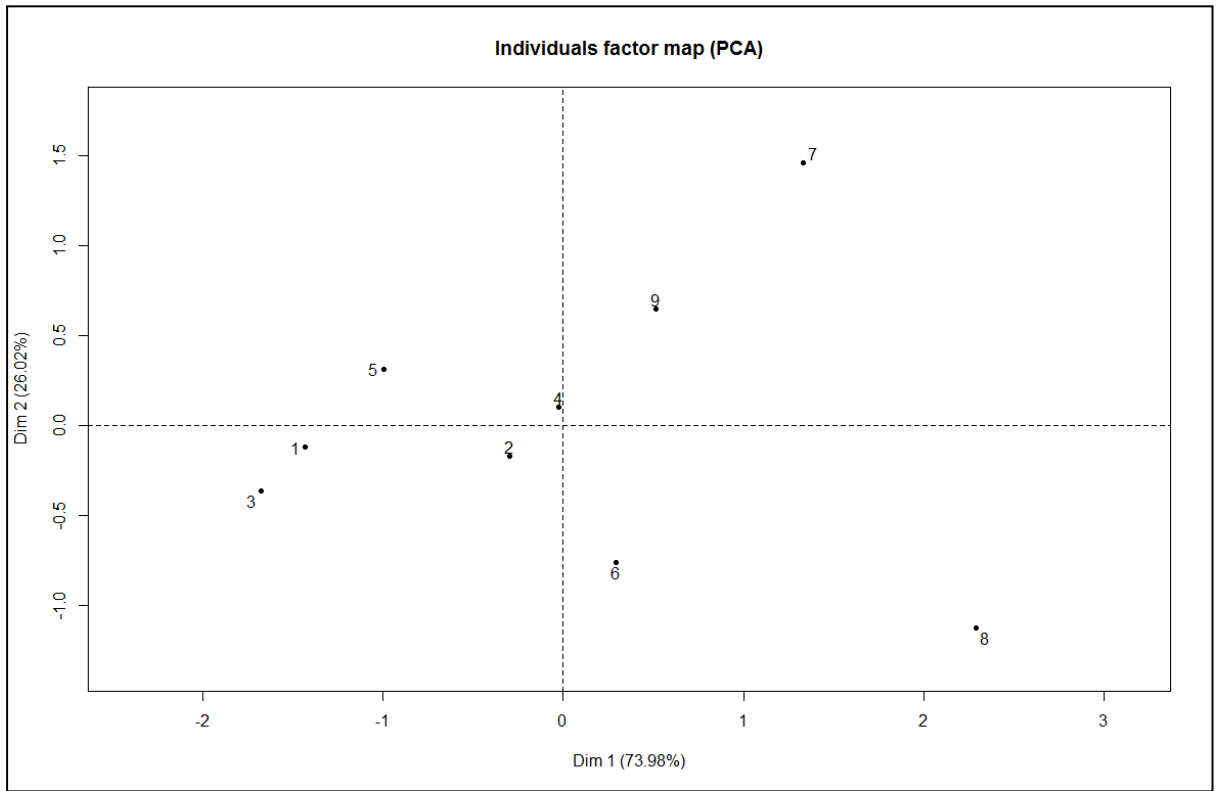


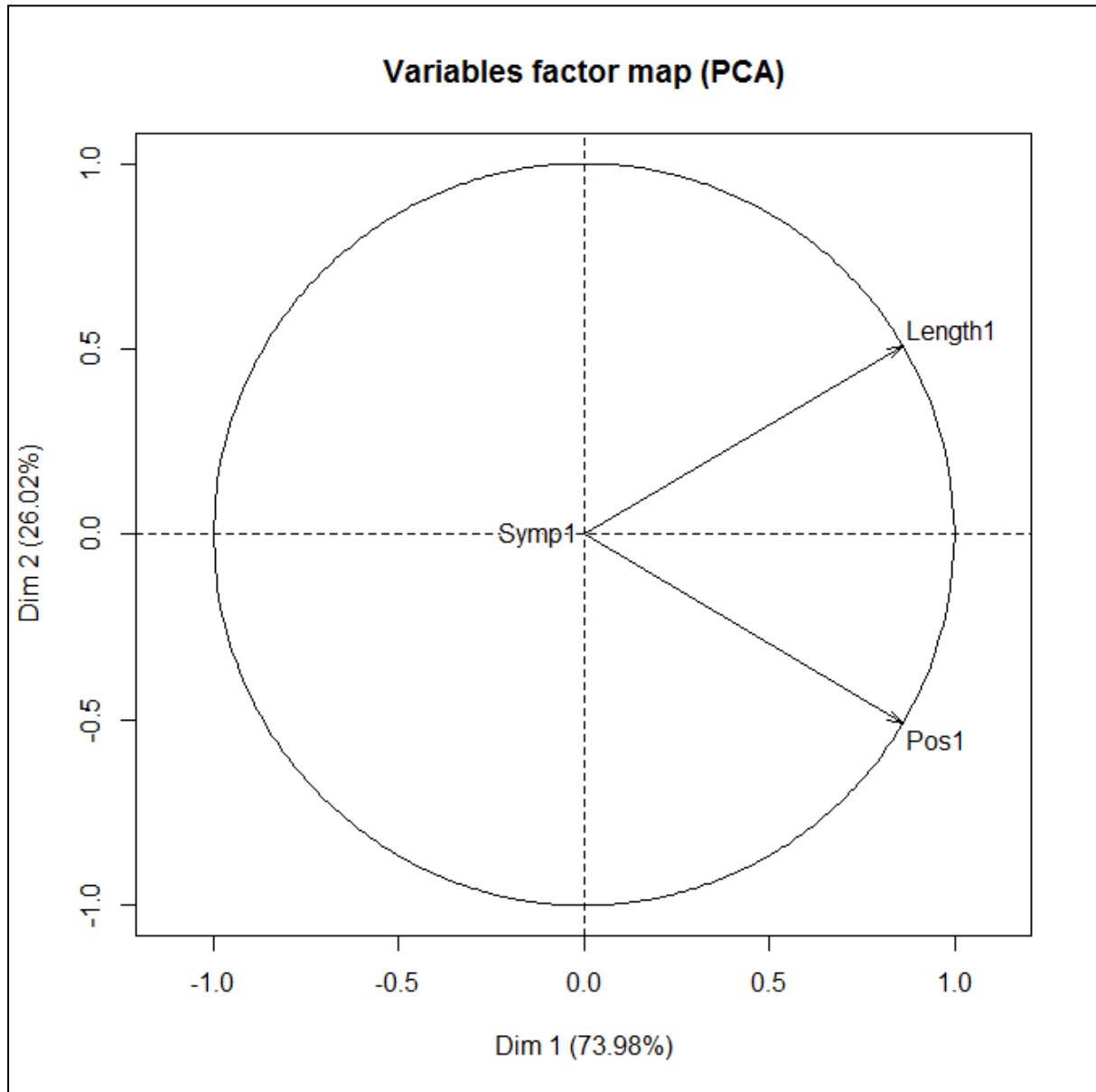
5. Procedure 5

No analysis could be performed as there are only 4 observations in this subgroup.

6. Procedure 6

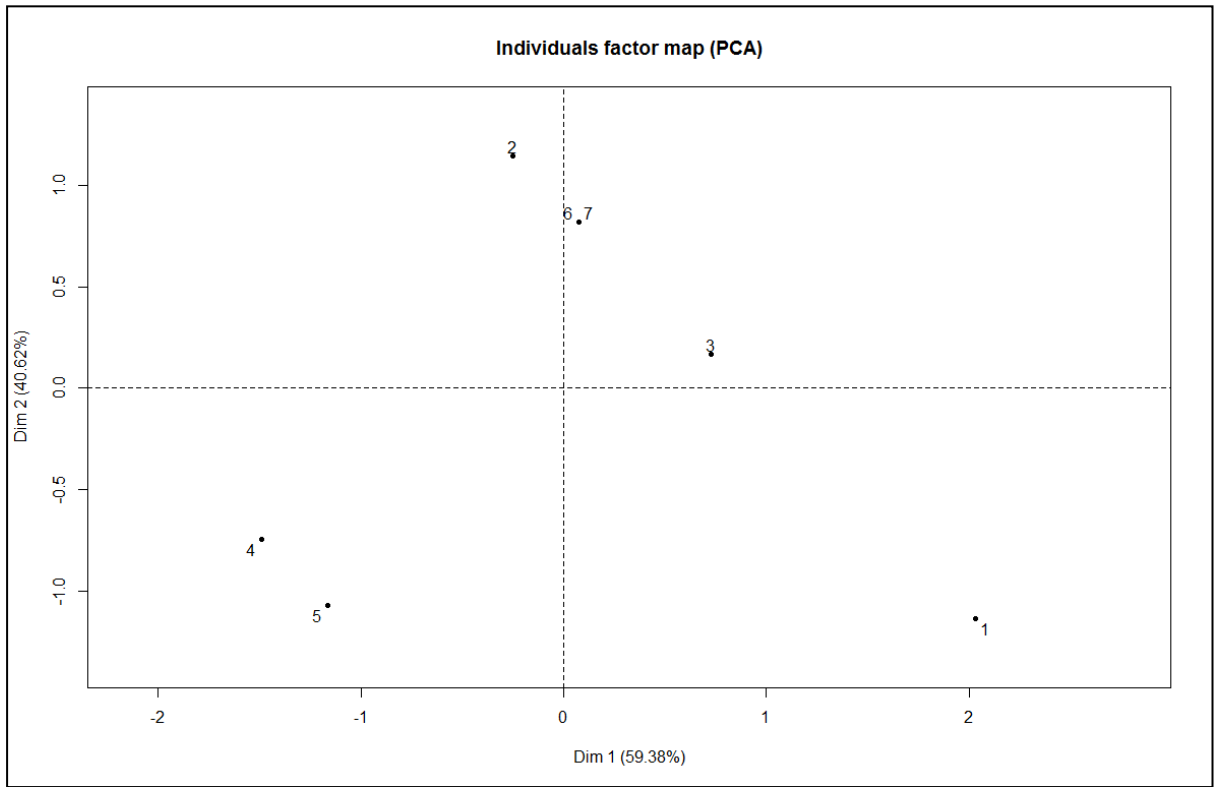
	Eigenvalue	Percentage of variance	Cumulative percentage of variance
Stricture length	1.4795496	73.97748	73.97748
Stricture position	0.5204504	26.02252	100.00000
Presenting symptom	0.0000000	0.00000	100.00000

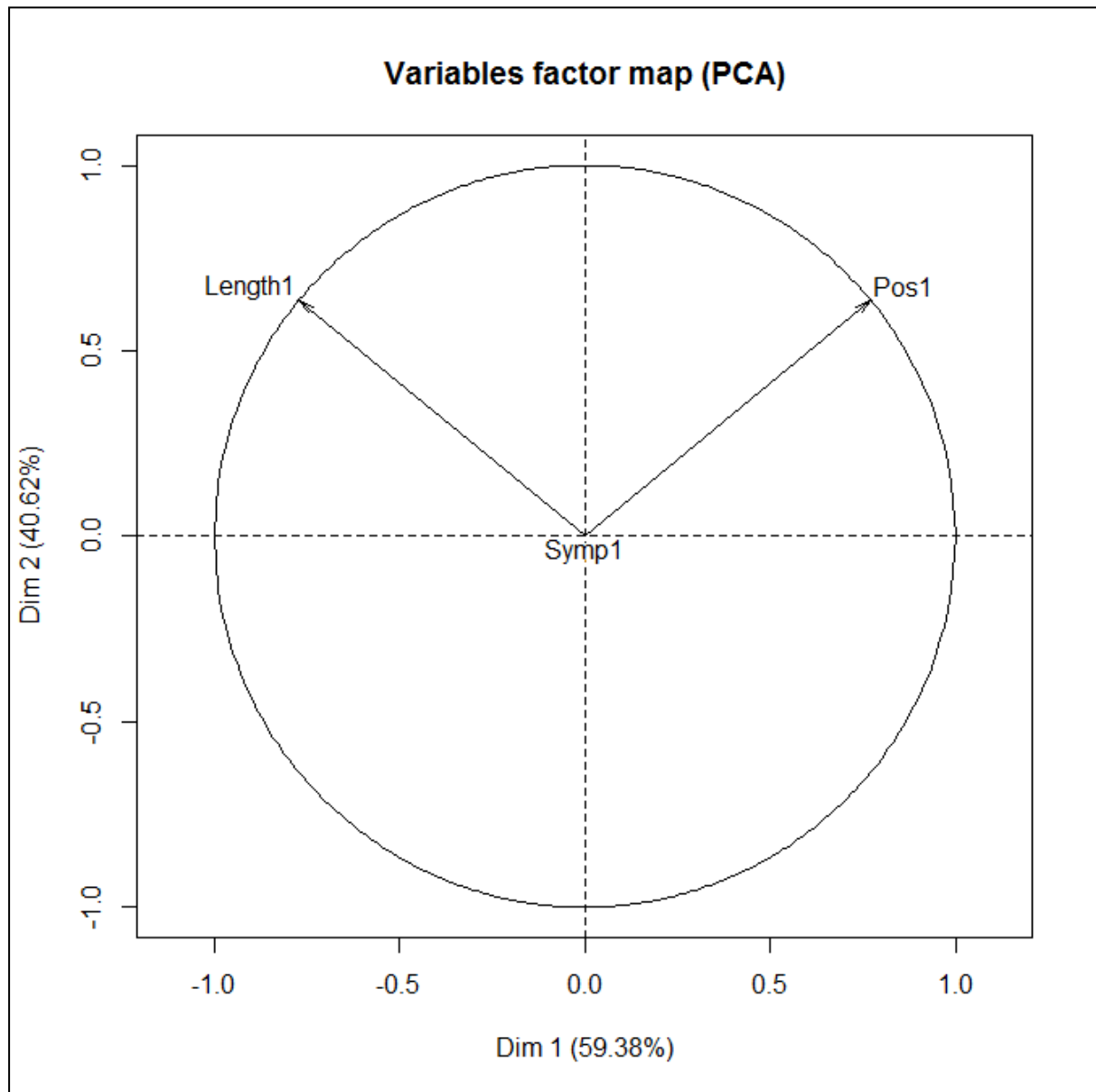




7. Procedure 7

	Eigenvalue	Percentage of variance	Cumulative percentage of variance
Stricture length	1.187663	59.38315	59.38315
Stricture position	0.812337	40.61685	100.00000
Presenting symptom	0.000000	0.00000	100.00000





8. Procedure 8

	Eigenvalue	Percentage of variance	Cumulative percentage of variance
Stricture length	1.8586877	61.95626	61.95626
Stricture position	0.7253553	24.17851	86.13477
Presenting symptom	0.4159570	13.86523	100.00000

