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Natural history of post-prostatectomy vesicourethral anastomotic strictures treated by transurethral resection

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TABLE OF CONTENTS

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DEDICATION

To my wife, my family

ZUSAMMENFASSUNG

Die Striktur der vesikourethralen Anatomose (VUAS) ist eine weltweit bekannte schwerwiegende Komplikation nach radikaler retropubischer Prostatektomie (RRP) mit einer in der Literatur berichteten Häufigkeit von 0,4-32% [1, 2]. Obwohl mehrere Theorien vorgeschlagen und geforscht wurden, ist die Therapie der VUAS bisher noch nicht klar standardisiert, da es bis heute keine ausreichende strukturierte Untersuchung zu den Folgen der verschiedenen Therapiemöglichkeiten gibt. Minimal-invasive endoskopische Chirurgie wird oft als Initialtherapie bevorzugt, hat jedoch ein sehr hohes Rezidivrisiko [3, 4]. Obwohl ein geringeres Rezidivrisiko bei alternativ offen-rekonstruktivem Eingriff besteht, der bei Fällen der fehlgeschlagenen endoskopischen Versorgung empfohlen wird, ist dieses Verfahren mit einer hohen postoperativen Morbidität durch eine anschließende Harninkontinenz verbunden [5-7]. Nichtdestotrotz besteht bisher kein klarer Konsensus darüber, welchen Patienten ein endoskopischer und welchen ein offen-rekonstruktiver Eingriff angeboten werden sollte. Dies ist auf den Mangel an validen Daten zum klinischen Verlauf der Patienten nach endoskopischer Therapie zurückzuführen.

Diese retrospektive Studie mit einem mittleren Follow-up von 36,1 Monaten von 60 Patienten (Durchschnittsalter 65,5 Jahren), die mittels einer endoskopischen transurethralen Resektion der Anastomosenstriktur (TUR-AS) in der Urologischen Klinik und Poliklinik des Klinikum Großhadern der Universität München behandelt wurden, wurde mit dem Ziel der Identifizierung des natürlichen Verlaufs dieser häufigen Komplikation durchgeführt, durch ausführliche Analyse der Patientendaten, Pathologie

des Tumors, Häufigkeit von Rezidiven der Striktur und Anzahl folgender Eingriffe und Art von erneuten Eingriffen bis zum Erreichen einer dauerhaften Lösung der Erkrankung. Rezidivstrikturen nach der ersten TUR-AS wuden im Rahmen der Nachuntersuchung dokumentiert und mittels erneuter TUR-AS behandelt. Bevor eine dritte TUR-AS geplant wurde, wurde ein offen-rekonstruktives Verfahren angeboten.

Der Median der Rezidivstrikturen betrug 1, mit 11 maximalen Strikturen ohne signifikantes Rezidivmuster. Das mittlere Zeitintervall zwischen RRP and erster Entstehung einer VUAS betrug 10,5 Monaten und Patienten entwickelten Rezidivstrikturen in einem mittleren Zeitintervall von 5,2 Monaten. Diese Ergebnisse zeigen im Vergleich zu den Vorberichten [1, 8], einen späteren Zeitpunkt des Rezidivs. Obwohl mehr als zwei Drittel (73,3%) der Patienten nach der initialen TUR-AS und 61,3%-75% nach jedem aufeinanderfolgenden Eingriff ein Rezidivstriktur entwickelten, blieben 75% der Patienten nach einer oder mehreren Therapien strikturfrei. Bevor eine dritte TUR-AS geplant wurde, wurde ein offen-rekonstruktives Verfahren angeboten und dies bei 21,7% der Patienten durchgeführt. Es ist wichtig zu erwähnen, dass 61% dieser Patienten mit adjuvanter Strahlentherapie behandelt wurden, die als Risikofaktor für die Entwickelung von Strikturen und Rezidivstrikturen dokumentiert wurde [5]. Bezüglich funktioneller Ergebnisse und Harninkontinenz wurden bei Patienten, die keinem offenen Verfahren unterzogen hatten, bei der letzten Nachuntersuchung durchschnittlich 2,2 (IQR 0-10) Einlagen/Tag verwendet.

Obwohl ein hohes Rezidivrisiko nach initialer TUR-AS und ein signifikanter Einfluss auf die Lebensqualität der Patienten beobachtet wurden, konnte auch nach mehreren endoskopischen Eingriffen eine dauerhafte Rezidivfreiheit erreicht werden. Das steht im

Gegensatz zu klassischen Harnröhrenstrikturen und unterstützt bei dieser Erkrankung eine Strategie der wiederholten endoskopischen Therapien auch nach mehreren Rezidiven, sodass auf offen-rekonstruktive Techniken – mit deren hohem Inkontinenzrisiko – nur in Ausnahmefällen zurückgegriffen werden muss. Daher ist eine sorgfältige Auswahl der Behandlung erforderlich, und die Entscheidung, ob dem Patienten eine endoskopische transurethrale Therapie oder eine mit hohem Risiko verbundene offen-rekonstruktive Operation angeboten werden soll, sollte individuell getroffen werden.

Dennoch sind weitere Studien und Follow-ups erforderlich, um den genauen Verlauf besser zu verstehen und somit die Entwicklung dieser Komplikation zu verhindern. Die Erkenntnisse dieser Studie stützen sich auf eine große Patientenzahl, die in Hinblick auf relevante Parameter untersucht wurden. Trotz der großen Anzahl von 60 Patienten, die ein im Vergleich zur bisher verfügbaren Literatur dieser Komplikation ein sehr großes Kollektiv ist, und der Beschränkungen bei dem retrospektiven Design, fehlenden Daten bezüglich weiterer Strikturtherapien, des intraoperativen Blutverlusts, der Extravasation von Urin nach RRP und des Lebensstils der Patienten, beschreibt diese Studie erstmals den gesamten Verlauf der Erkrankung über mehrere Eingriffe.

ABSTRACT

Vesicourethral anastomotic strictures (VUAS) are a globally well-recognized complication following radical prostatectomy (RP), with reported incidence rates varying from 0.4% to 32% [1, 2]. Although many hypotheses have been proposed and investigated, the precise treatment of this complication is still unclear. Endoscopic surgery is often preferred as the initial treatment approach [3, 4] but is burdened by a high risk of stricture recurrence. Alternative open reconstructive surgery, which bears a very high risk of urinary incontinence, is reserved for cases in which repeated endoscopic procedures have failed [5-7]. However, to date there is no clear consensus which patients should be offered an endoscopic or an open reconstructive approach. This is due to the lack of data on the individual risk of recurrence in patients who are treated by recurrent endoscopic procedures.

This retrospective study with a mean follow-up of 36.1 months of 60 patients (mean age 65.5 years), who underwent endoscopic transurethral resection of the anastomotic stricture (TUR-AS) in the University Hospital Munich, Großhadern, was carried out with the objective of identifying the natural course of this well-documented complication by analysing patient characteristics, tumor pathology and VUAS recurrences. Follow-up examinations after initial TUR-AS documented stricture recurrence, in which case patients underwent repeated TUR-AS. Before performing a third endoscopic resection, open reconstructive surgery was proposed.

The median of VUAS recurrences was found to be 1, with a maximum of 11 times without any significant pattern of recurrence. The mean time interval between RP and

first VUAS formation was 10.5 months and patients developed VUAS recurrences at a mean time interval of 5.2 months. These findings demonstrate, in comparison to prior reports [1, 8], a later recurrence time point. Although more than two thirds (73.3%) of patients suffered from recurrence after the initial TUR-AS, and 61.3-75% had recurrent VUAS after every consecutive intervention, 75% of patients were stable after one or more treatment. Before a third TUR-AS was performed, open reconstructive surgery was proposed and performed in 21.7% of the patients. It is essential to mention, that 61% of these patients had adjuvant radiotherapy, which has been vastly documented as risk factors for the development of TUR-AS and its recurrence [5]. Regarding functional outcomes in terms of urinary incontinence, in patients who did not undergo open surgery, there was a mean use of 2.2 (IQR 0-10) pads/day at the last follow-up.

Although a high risk of recurrence after initial TUR-AS and a significant impact on patients' quality of life were observed, a stricture-free status could be achieved even after multiple endoscopic treatments. This finding is in contrast to respective results from patients with primary urethral stricture disease without prostatectomy in their history. Therefore, careful treatment selection is required in these patients, and the decision of whether to offer transurethral treatment or high risk associated open reconstructive surgery to the patient should be suited individually.

Nonetheless, further studies and follow-ups are needed to better understand the precise course and therefore prevent the development of this complication. Despite the large number of 60 patients, this study was limited to the retrospective design and did not have sufficient information regarding further TUR-AS treatments, intraoperative blood loss, extravasation of urine after RP, or patients' lifestyle.

LIST OF FIGURES

LIST OF GRAPHS

LIST OF TABLES

LIST OF ABBREVIATIONS

VUAS	Vesicourethral anastomotic stricture
RRP	Radical retropubic prostatectomy
TUR-AS	Transurethral resection of the anastomotic stricture
PCa	Prostate cancer
RP	Radical prostatectomy
RT	Radiotherapy
AS	Active surveillance
WW	Watchful waiting
TUR-P	Transurethral resection of the prostate
TNM	Tumor, node and metastasis
BCR	Biochemical recurrence
EBRT	External beam radiotherapy
GS	Gleason score
EAU	European Association of Urology
PSA	Prostate-specific antigen
DRE	Digital rectal examination
MRI	Magnetic resonance imaging
mpMRI	Multi-parametric magnetic resonance imaging
DCE	Dynamic contrast-enhanced
PIN	Prostatic intraepithelial neoplasia
ADT	Androgen-deprivation therapy
DVT	Deep venous thrombosis

PE	Pulmonary embolism
ED	Erectile dysfunction
RALP	Robot-assisted laparoscopic prostatectomy
AS	Anastomotic stricture
NVB	Neurovascular bundle
HDR	High-dose-rate
BNC	Bladder neck contracture
mL	Millilitre
Qmax	Maximum urinary flow rate
PPI	Postprostatectomy incontinence
UI	Urinary incontinence
PDE5	Phosphodiesterase type 5
IQR	Interquartile range
CRP	C-reactive protein
AUA	American Urology Association
POD	Postoperative day
SIU	Société International d'Urologie
DVIU	Direct vision internal urethrotomy
LUTS	Lower urinary tract symptoms
iPSA	Initial PSA

I. INTRODUCTION

Abnormalities in prostate growth can lead to one of the most commonly diagnosed cancers worldwide. Many treatment plans, including conservative and operative approaches, have been proposed, in order to combat prostate cancer. In spite of advances in treatment of prostate cancer in recent years, surgical techniques such as postprostatectomy anastomotic strictures (PPAS), remain a relatively common complication. Vesicourethral anastomotic strictures (VUAS) are considered to be one of the most common complications following radical retropubic prostatectomy (RRP), with rates ranging up to 32% [9, 10]. Retrospective studies have reported that the majority of VUASs present within the first 24 months following RRP with lower urinary track symptoms, such as reduced stream or ultimate retention of urine [8, 10, 11]. While the incidence of this common postoperative complication is well documented, there is no consensus regarding the optimal treatment of this complication [8, 12]. One of the most common treatment options is the transurethral resection of the anastomotic stricture (TUR-AS), which bears a high risk of stricture recurrence [8, 10]. Although this option seems to be popular, there is no data available in current literature on further stricture recurrence rates and impact on urinary continence after repeated TUR-ASs. The objective of this study is to present functional outcomes of repeated TUR-ASs of VUAS in terms of recurrence rates and data on urinary continence.

I.1 Prostate cancer

With 70,000 new occurring cases each year and a median age of diagnosis of 66 years, prostate cancer (PCa) ranks third among the causes of cancer deaths in Germany and second in the USA and UK [13-17].

The introduction of screening for PCa by regular determination of prostate-specific antigen (PSA) has allowed an early detection and treatment of the disease [14, 15]. Whether the stage shift in PSA-detected cancers differs by Gleason score or not, the widespread PSA screening has led to a stage shift from advanced carcinomas to localized, well-differentiated tumors that rarely have an impact on life expectancy [14, 15, 18].

More often than not, early disease presents with no typical symptoms and diagnosis is based on abnormal PSA levels and / or digital rectal exam, followed by a transrectal ultrasound-guided biopsy, or both [17]. In order to evaluate prognosis and determine the patient-specific treatment approach, disease staging using a number of systems is applied. PCa screening biomarkers may also be useful as prognostic factors [17, 19]. Associated harms and costs of overdiagnosis and overtreatment of low-risk tumors that may not have caused harm must be observed and prevented during the approach to PCa treatment and policies must be tailored to limit any potential damages [15, 17, 20, 21]. The objective of treatment is to identify patients who are most likely to gain from therapy while minimizing treatment-related side effects and complications [17, 22]. Treatment options vary from radical prostatectomy (RP) and radiotherapy (RT) for intermediate- and high-risk tumors to additional active surveillance (AS) and watchful waiting (WW) for low-risk tumors and palliative indications [14, 17, 23, 24].

I.1.1 Classification systems

The clinical staging of PCa is based on the tumor, node and metastasis (TNM) classification system, which has undergone numerous modifications since its first adoption in 1975 (**Table I.1.1.1**) [25]. In the most recent update, the TNM stage is combined with PSA level and Gleason score (GS) to classify newly diagnosed cases into prognostic groups [22].

T – Primary Tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable or visible by imagine
T2	Tumor confined within the prostate[1]
T3	Tumor extends through the prostatic capsule[2]
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N – Regional lymph nodes[3]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis[4]
M – Distant metastasis[5]	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table I.1.1.1: Tumor Node Metastasis (TNM) classification of PCa [25].
[1] *Tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.*
[2] *Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.*
[3] *The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries.*
[4] *Laterality does not affect the N-classification*
[5] *When more than one site of metastasis is present, the most advanced category should be used.*

Another classification system is the EAU risk group classification system, which is based on the grouping of patients with a similar risk of postoperative biochemical recurrence (BCR) or external beam radiotherapy (EBRT) (**Table I.1.1.2**) [23].

	Low-risk	**Intermediate-risk**	**High-risk**	
Definition	PSA < 10 ng/mL and GS[1] < 7 and cT1-2a	PSA 10-20 ng/mL or GS[1] 7 or cT2b	PSA > 20 ng/mL or GS[1] > 7 or cT2c	any PSA any GS[1] cT3-4 or cN+
	Localised			**Locally advanced**

Table I.1.1.2: EAU Risk groups for biochemical recurrence of localized and locally advanced PCa [23].
[1] *GS = Gleason score*

I.1.2 Diagnostic Evaluation

I.1.2.1. **Screening and early detection**

According to the European Association of Urology Guidelines (EAU), an individualized risk-adapted strategy for early detection might be considered. It is essential to identify the individuals who are most likely to benefit from early diagnosis, taking into account the potential overdiagnoses and harms involved. In order to reduce the number of unnecessary biopsies, risk calculators may be useful in helping to determine what the potential risk of PCa may be [23]. Although the value of PSA screening remains controversial and mass screening of PCa is not indicated from a public health point of view, patients who present for health examinations should be made aware of the possibility of early diagnosis on an individual basis based on digital rectal examination (DRE) and PSA testing, so that they can make an informed decision about the need for routine screening [22, 23].

I.1.2.2. **Clinical diagnosis**

Suspicion of PCa is usually based on pathological DRE and/or PSA levels. A definitive diagnosis is reliant upon histopathological verification of adenocarcinoma in prostate biopsy cores or specimens from transurethral resection of the prostate (TUR-P) [17].

I.1.2.3. **Histopathology**

Adenocarcinomas represent more than 95% of primary PCa and are frequently multifocal and heterogeneous in patterns of differentiation [26]. Prostatic intraepithelial neoplasia (PIN) is often present in association with prostatic adenocarcinomas [26, 27]. PIN is subdivided into low grade and high grade forms, with the high-grade form having the ability to be a precursor for adenocarcinoma [27]. The remaining few percentages of cases are considered to be rare tumors such as small-cell tumors, intralobular acinar carcinomas, ductal carcinomas, clear cell carcinomas and mucinous carcinomas [28]. The histologic grade of prostate adenocarcinomas is usually reported according to one of the variations of the Gleason scoring system which is calculated based on the degree of architectural differentiation, from a well differentiated grade 1 to a poorly differentiated grade 5 [28, 29]. These grade groups represent a compression of multiple different Gleason scores (**Table I.1.2.3.1**), where the classical score is derived by adding the two most prevalent pattern grades, yielding a score ranging from 2 to 10 [23, 26]. The histologic differentiation of Gleason scores (**Tab I.1.2.3.2**) is often provided by its separate components, such as Gleason 3 + 4 = 7, due to the fact that there is some evidence that the least-differentiated component of the specimen may provide independent prognostic information [26].

Gleason score	Grade group
2-6	1
7 (3 + 4)	2
7 (4 + 3)	3
8 (4 + 4) or (3 + 5) or (5 + 3)	4
9-10	5

Table I.1.2.3.1: International Society of Urological Pathology 2014 grade groups [23].

Gleason score	Description
Gleason X	Gleason score cannot be processed
Gleason ≤6	Well differentiated (slight anaplasia)
Gleason 7	Moderately differentiated (moderate anaplasia)
Gleason 8-10	Poorly differentiated/undifferentiated (marked anaplasia)

Table I.1.2.3.2: Histologic differentiation of Gleason scores [26, 30].

I.1.3 Management

I.1.3.1. **Overview**

The initial evaluation of and treatment discussion with a patient with PCa focus on the patient's overall life expectancy and overall health status as well as the biologic characteristics of the tumor, together with its predicted aggressiveness and behaviour [31]. Life expectancy, rather than patient age, is a major factor to consider in treatment selection [29, 32]. The patient's overall health status includes both patient and family history as well as the present state of the patient's well-being and the degree of any coexistent disease [29]. The decisions regarding treatment should take into account the preferences of the patient for the various treatment options, with consideration of complications, adverse effects, compliance, relative efficacy and quality-of-life issues [29]. **Table I.1.3.1.1** offers an overview of the diverse treatment options [33].

	Prostate cancer	Treatment options
Non-metastatic PCa[3]	Localized PCa[3]	Watchful waiting Active surveillance Radical prostatectomy External beam radiotherapy Brachytherapy Lymphadenectomy HIFU[1] therapy
	Locally advanced PCa[3]	Radical prostatectomy External beam radiotherapy HDR[2] Brachytherapy Lymphadenectomy Adjuvant percutaneous radiation
Recurrent or metastatic PCa[3]	PSA[4]-recurrent PCa[3]	Watch and wait Salvage radiotherapy
	PSA[4] progression	Salvage radical prostatectomy HIFU[1] therapy
	Metastatic hormone-sensitive PCa[3]	Androgen deprivation therapy Chemotherapy with Docetaxel Maximum androgen blockade
	Androgen-independent PCa[3]	Chemotherapy
	Bone metastases	Pain management Radiotherapy Bisphosphonate Denosumab Radiopharmaceuticals Chemotherapy

Table I.1.3.1.1: Treatment overview extracted from AWMF Guidelines [33].
[1] *HIFU = High Intensity Focused Ultrasound*
[2] *HDR = High-dose-rate*
[3] *PCa = Prostate cancer*
[4] *PSA= Prostate-specific antigen*

I.1.3.2. Deferred treatment

The deferred treatment using distinct strategies such as active surveillance (AS) and watchful waiting (WW) (**Tab I.1.3.2.1**) for conservative management aims to reduce overtreatment [23].

AS is a management strategy used for early-stage PCa designed to balance early detection of aggressive forms and overtreatment of indolent disease [34]. The purpose of AS is to achieve correct timing for curative treatment while taking individual life expectancy into consideration, rather than delayed application of palliative treatment [23, 34]. Patients with lower risk tumors that have low Gleason score, PSA level and clinical stage as well as patients with a shorter life expectancy could be candidates for the AS treatment strategy [29].

WW is based on the premise that some patients will not benefit from definitive treatment of the primary PCa [29, 32]. The management strategy of WW is characterized through the careful monitoring of patient's condition without subscribing any treatment until the development of local or systemic progression with disease-related complaints appears [23]. Treatment is then given to relieve symptoms and improve quality of life [23].

	Active surveillance	**Watchful waiting**
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, re-biopsy, mpMRI	Not predefined
Aim	Minimize treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Comments	Only for low-risk patients	Can apply to patients with all stages

Table I.1.3.2.1: Definitions of active surveillance and watchful waiting [23].

I.1.3.3. **Surgery**

There is no better way to cure cancer that is confined to the prostate than total surgical removal [22]. Radical prostatectomy (RP) is one of the reference treatments for localized PCa and it involves the removal of the entire prostate gland between the urethra and bladder [23, 35]. While a variety of surgical approaches such as open retropubic approach, perineal, transperitoneal or extraperitoneal laparoscopic approach, robotic assisted or not, are available, the goal of RP by any approach must be eradication of disease, while preserving continence and, whenever possible, potency [23, 35, 36]. It has been shown that RP is the only form of treatment for localized PCa that reduces progression of metastases and death from the disease and therefore remains the gold-standard treatment for clinically localized PCa in patients with at least 10 years of life expectancy [22, 23, 35, 37, 38]. Compared to watchful waiting and radiotherapy, RP remains the only treatment modality where there is published evidence of survival advantage; furthermore, it has the benefit of sampling lymph nodes intraoperatively when compared to external beam radiotherapy (EBRT) [39, 40].

Although surgery and the various surgical approaches can be difficult and may have significant morbidity, especially in terms of erectile dysfunction (ED) and incontinence, which potentially has a great impact on quality of life, recent surgical advances, such as robot-assisted laparoscopic prostatectomy (RALP), have shown encouraging results with minimized associated morbidity and maximized quality of life while still achieving surgical care [23, 39].

Both the traditional surgical approach of RRP and the newly developed RALP techniques have technical pros, cons and qualities that may reflect on postoperative urinary and sexual function, and intra- and perioperative complications (**Table I.1.3.3.1**) [41]. The evaluation and comparison of the RP techniques can be difficult, but it is likely that the surgeon’s experience, rather than the surgical approach, can best determine the surgical results, and therefore there is no reason that a surgeon obtaining excellent functional and oncologic results with RRP should switch to a different approach [42].

Predicted probability of event	RALP (%)	RRP (%)
BNC/AS	1.0	4.9
Anastomotic leak	1.0	3.3
Infection	0.8	4.8
Organ injury	0.4	0.8
Ileus	1.1	0.3
DVT	0.6	1.4
Predicted probability of event	**RALP (%)**	**RRP (%)**
Clavien I	2.1	4.2
Clavien II	3.9	17.5
Clavien IIIa	0.5	1.8
Clavien IIIb	0.9	2.5
Clavien Iva	0.6	2.1
Clavien V	< 0.1	0.2

Table I.1.3.3.1: Intra- and perioperative complications of RRP and RALP [23, 43].
RRP = Radical retropubic prostatectomy
RALP = Robot-assisted laparoscopic prostatectomy
BNC = Bladder neck contracture
AS = Anastomotic stricture
DVT = Deep venous thrombosis

I.1.4 Radical retropubic prostatectomy

I.1.4.1. **Overview**

Radical retropubic prostatectomy (RRP) is the gold-standard and most common procedure for prostatectomy worldwide, and it is considered to be one of the most challenging operations in the field of urology [22]. RRP involves the removal of the entire prostate between the urethra and bladder, the resection of both seminal vesicles, along with sufficient surrounding tissue to obtain negative margins, and a pelvic lymph node dissection if there is significant risk of lymph node involvement [23, 44]. Great skill and experience in the selection of surgical candidates and operative technique are crucial to achieve complete cancer removal with negative surgical margins, preservation of urinary continence, early recovery of erectile function, minimal blood loss and no perioperative complications, which are the goals of surgery [22, 45].

The increased surgical experience has lowered the complication rates as well as the intraoperative and postoperative morbidity of RP, and improved cancer cure [46-49].

I.1.4.2. **Surgical anatomy and technique**

It is necessary to have a complete understanding of the prostate veins to avoid excessive bleeding and to ensure a bloodless field in exposing the membranous urethra and the apex of the prostate (**Figure I.1.4.2.1**) [22]. The veins of the prostate drain into the Santorini plexus [22]. The deep dorsal vein leaves the penis under the Buck fascia between the corpora cavernosa and penetrates the urogenital diaphgram, dividing into three major branches: the superficial branch and the right and left lateral venous plexuses [50].

Before branching to the seminal vesicle and the base of the bladder and prostate, the inferior vesical artery supplies arterial blood to the prostate through the urethral and capsular prostatic vessels [22].

The location of the capsular vessels can help identify the nerve branches innervating the prostate, which arise from the pelvis plexus and travel in the lateral pelvic fascia dorsolaterally between the prostate and rectum. These structures have been termed the neurovascular bundle (NVB) and are located in the lateral pelvic fascia between the prostatic fascia and the levator fascia [22].

The Denonvilliers fascia, the prostatic fascia and the levator fascia are the three layers that cover the prostate [22]. The Denonvilliers fascia is a fragile layer of connective tissue which must be completely excised in order to gain maximal surgical exposure, since it is not possible to distinguish between its anterior and posterior layers [22, 51]. The prostatic fascia is in direct contact with the parenchyma of the prostate on its anterior and anterolateral borders; on the lateral border, the prostatic fascia blends with the levator fascia, forming the lateral pelvic fascia [22, 52]. In contrast to radical perineal prostatectomy, when performing RRP, the approach to the prostate is from outside the complex fascial investments. Therefore, the lateral pelvic fascia must be divided and dorsal vein complex must be ligated [22, 53].

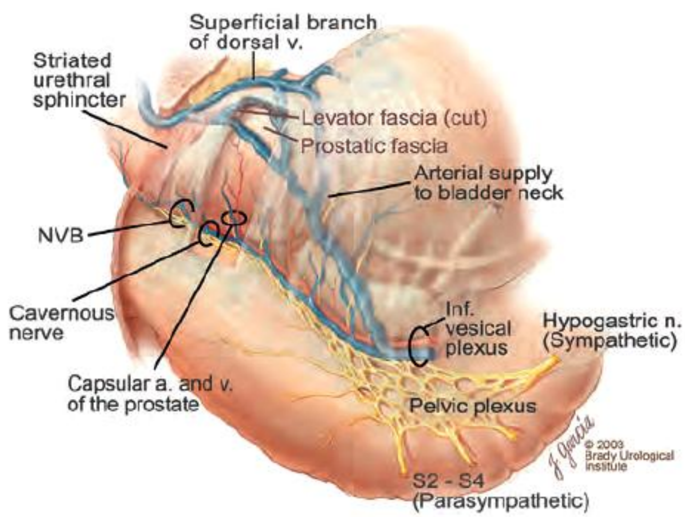


Figure I.1.4.2.1: A lateral view illustrating that the prostate receives its blood supply and autonomic innervation between the layers of the levator fascia and prostatic fascia.[22]
a. = artery, v. = vein, inf. = inferior, NVB = neurovascular bundle

The preoperative assessment should identify factors that may add to the technical challenge of the surgical procedure and the perioperative care; therefore, it must include a focused review of systems, a complete history, an inquiry of all medications, a physical examination and routine preoperative laboratory tests [22]. Life-threatening complications associated with RRP are uncommon and include myocardial infarction, cerebrovascular accident, cardiac arrhythmias, pulmonary embolus, haemorrhage, and anaesthesia reactions [22].

On the day of RRP (**Figure I.1.4.2.2**), the patient is placed in a supine position; the table can be flexed in obese men to increase the distance from the umbilicus to the symphysis, supplemented by a mild Trendelenburg position [54]. A lower abdominal midline incision is made extending from the pubis toward the umbilicus, the fasciae and rectus muscles are incised and separated, and the peritoneum is mobilized off the external iliac vessels to the bifurcation of the common iliac artery [22]. It is crucial to preserve the soft tissue covering the external iliac artery that contains the lymphatics draining the lower extremity to avoid lower extremity edeme and lymphocele formation [22]. After removing the retropubic fat, isolating and cauterizing the superficial branch of the dorsal venous complex and bluntly incising the pelvic fascia bilaterally, all residual muscle fibres have to be displaced from the lateral aspect of the prostate laterally to expose the prostatic fascia and the dorsal venous complex [55]. The dorsal venous complex is then divided using electrocautery, leaving a defect in the prostatic fascia, where an ‘inverted V’ incision is made, carrying the line of the incision distally and proximally [55]. After taking special care of the tissue immediately lateral to the prostatovesical junction, since this is the location of the NVB as it courses through the membranous urethra, the tissue could be spread using Statinsky scissors to carry the incision parallel to the NVB towards the bladder and urethra, moving the lateral prostatic fascia posteriorly and leaving it uninjured [55, 56]. The anterior Denonvilliers fascia attached to the posterior aspect of the prostate could be separated from the posterior Denonvilliers fascia attached to the anterior rectum by placing the index finger of the left hand between the prostatic fascia and the prostatic capsule and moving it under the posterior aspect of the prostate [55]. The tip of the left index finger is then moved toward the right prostatoapical junction, and extended toward the lateral prostatic fascia on the contralateral side, anterior to and above the right NVB. The right lateral prostatic fascia above the NVB can be clogged with a right-angle clamp by using the tip of the left index finger which is moved above the right NVB, as a guidance system [55]. By spreading the clamp, the right NVB can be detached from the prostate cranially and posteriorly, and the membranous urethra can be divided at the apex of the prostate using electrocautery at an angle of division that allows preservation of residual delicate fibres of the external urethral rhabdosphincter complex [55]. After dividing the urethra, mobilizing the prostate and ligating the lateral vascular pedicles, the anterior layer of Denonvilliers' fascia and the ampullae of the vas deferens are identified and dissected off the medial aspect of the seminal vesicles and divided after being mobilized distally [55]. The seminal vesicles and the ampullae of the vas deferens are then retracted cephalad, and dissected free of the bladder base and the posterior aspect of the bladder while preserving the circular fibres of the bladder neck [55]. The bladder neck is reconstructed with a running suture to approximate full-thickness muscularis, and incorporating the mucosa to avoid problematic hematuria, forming a tennis racquet closure [22]. The bladder mucosa is then attached onto the parietal bladder facia, and a direct vesicourethral anastomosis is achieved through the application of six evenly placed absorbable sutures guided by an urethral sound [55]. After meticulous exploration of the operative field for cause of bleeding, a new clot-free silicone Foley catheter is inserted through the bladder neck and irrigated with 15 mL of saline, without being placed on traction while tying the sutures [22]. In order to secure the position of the bladder while the sutures are tied, a Babcock clamp can be placed on the anterior bladder wall close to the reconstructed bladder neck, guaranteeing a superior coaptation of mucosa to mucosa and reducing the likelihood of bladder neck contractures [22]. The sutures are then tied, and manipulation of the Foley catheter can help ensure that it is not caught in one of them. Before final irrigation of the surgical site, the Foley catheter is inflated with saline to remove any clots [22].

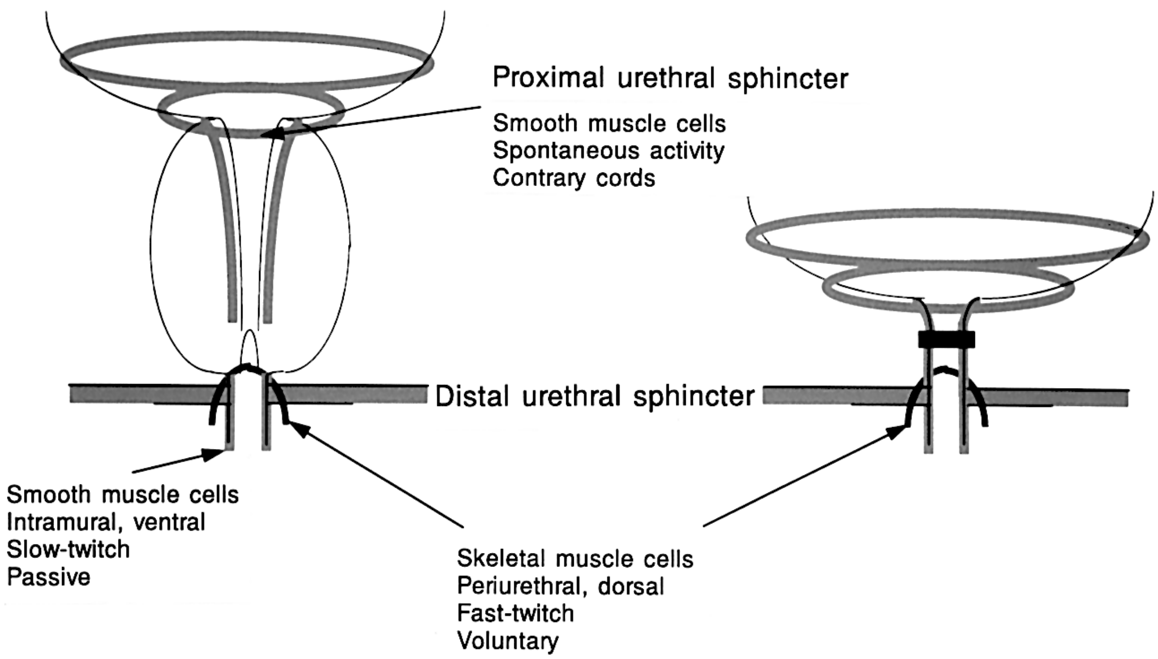


Figure I.1.4.2.2: Anatomical structures before and after RRP [4].

I.1.4.3. **Postoperative management**

Postoperatively, patients receive antibiotic prophylaxis and intravenous patient-controlled analgesia for pain control [22, 54]. The urinary catheter that is left in place for 7 to 10 days postoperatively, represents a source of significant inconvenience, and limits the return to daily activities and work; therefore, it should be removed as soon as possible without compromising outcomes such as urinary retention and bladder neck contracture [22, 57, 58]. A postoperative cystography under fluoroscopic control, by filling the bladder with a contrast agent until the patient experiences a sense of fullness and slight discomfort, allows an early removal of the urinary catheter when there is no extravasations while also identifying the small subset of patients who might benefit from longer bladder drainage [22, 54].

I.1.4.4. **Intraoperative complications**

The most common intraoperative complication is haemorrhage with an average blood loss between 300 to 1000 mL, usually arising from venous structures and can be controlled temporarily with packing, exposure, and suture or surgical clip ligation. Less common intraoperative complications include obturator nerve injury, rectal injury, and ureteral injury [22].

I.1.4.5. **Postoperative complications**

To ensure rapid recovery of each patient, early detection of complications and postoperative control is highly relevant [59]. Delayed hemorrhage is not considered a common complication of RRP and is managed cordially when it occurs, rarely requiring emergent exploration [22]. Nevertheless, patients presenting with severe hypotension after RRP and requiring acute transfusion may have pelvic hematoma drainage through the vesicourethral anastomosis and should be inspected early on to evacuate the pelvic hematoma in order to avoid symptomatic bladder neck contractures and long-term issues with urinary control [22, 60]. Other than hemorrhage, postoperative complications include DVT, bladder neck contracture, urinary incontinence, erectile dysfunction, peritonitis, ileus, nerve injury, intestinal injury, rectovesical fistula, infections, lymphocele, and inguinal hernia [59].

I.1.5 Vesicourethral anastomotic strictures

I.1.5.1. **Overview**

Bladder neck contracture, bladder neck stenosis, and anastomotic stenosis are synonymous terms for stricture at the level of the anastomosis between the bladder and membranous urethra (vesicourethral anastomosis). Vesicourethral anastomotic strictures (VUAS) are a well-recognized complication following RRP, occurring in rates varying between 0.4% and 32% of patients, and arising from inadequate coaptation of the mucosal surfaces due to inadequate approximation at the time of surgery, urinary exravasation, or distraction of the bladder neck from a hematoma [1, 2, 4, 22, 61-63]. Although VUASs usually occur after surgical interventions, they are highly associated with radiation therapy and ablative therapy for PCa; among the various radiation therapy modalities, high-dose-rate (HDR) brachytherapy has demonstrated the highest rate of stricture formation following RRP [64]. Most VUASs after RP occur within 2 years, with 66% appearing in the first 6 months of surgery [1, 65].

Bladder neck contracture (BNC) can be caused by scar tissue narrowing and enclosing the reconstructed bladder neck, resulting in symptoms of urinary frequency, urgency, poor stream, incomplete emptying of the bladder, and, in some cases, acute urinary retention. These symptoms do not only affect quality of life but cause patients to seek treatment with either dilatation, often multiple transurethral resections of the anastomotic stricture (TUR-AS), transurethral incision, or open surgery [4, 61].

While many factors contributing to formation of strictures have been discussed, one of the strongest predictors for subsequent development of VUAS was surgical approach, with reports of minimally invasive laparoscopic and robot-assisted laparoscopic technique to have a lower incidence of VUASs when compared to open surgery [66-68]. Possible reasons, such as better visualization whilst performing anastomosis allowing more accurate mucosal apposition, a continuous suturing technique, and overall reduced intraoperative blood loss, have been discussed for the difference seen between open and laparoscopic approaches [67, 69].

Higher rates of post-radical-prostatectomy VUASs have been reported in smokers, patients with ischemic heart disease, hypertension, diabetes, previous TUR-P, and a propensity to undergo hypertrophic scarring [1, 2, 8, 70]. Other technical factors discussed to be associated with the development of VUASs include degree of blood loss and hematoma formation, caliber of the reconstructed bladder neck, early urinary retention following catheter removal, and urinary extravasation [1, 2, 71-73]. Studies have shown that clearly, the development of VUASs following RRP is not due to one single factor but is a result of a complex interplay between patient characteristics and technical factors [10].

Lower urinary tract symptoms of VUASs, such as reduced stream or ultimate retention of urine, typically present within 6 months following RRP and require diagnostic investigations that usually reveal a reduced maximum urinary flow rate (Qmax) and an obstructive pattern on uroflowmetry following which the diagnosis is made at urethrocystoscopy with the findings of strictures [8, 10, 61, 74]. The diagnosis should be suspected in patients with poor urinary stream or prolonged unexplained incontinence, and VUASs may alternatively present with or come to light during the workup for postprostatectomy incontinence (PPI) [10, 22, 63].

I.1.5.2. **Treatment**

Although many treatment options have been proposed, a universally accepted protocol for managing anastomotic strictures does not currently exist and the optimum treatment for contractures seems to be controversial. Many have suggested transurethral procedures such as transurethral balloon dilatation, dilatation using the Nottingham dilators followed by a 3-month self catheterisation protocol, initial dilatation with repeat dilatation as needed for an interval of 6 months and resection, initial dilatation and subsequent cold knife urethrotomy, endoscopic resection using electrocautery, and injection of triamcinolone acetonide at the bladder neck after cold-knife incision in patients with recalcitrant VUASs [1, 4, 8, 10, 22, 62, 75].

Endoscopic management is considered to be first-line treatment for most VUAS following RP. While simple dilation using catheters or bougies is often performed as the initial treatment modality, its success rate has varied [9, 76, 77]. One of the most commonly performed surgical techniques to achieve transurethral resection of anastomotic strictures is cold-knife incision, in which the stricture scar is incised with a knife endoscopically. Although it has a high recurrence rate, it is suited for patients who refuse surgical treatment or are unsuited for surgery for other reasons [22, 74, 78-81].

Open reconstructive retropubic, perineal or abdominoperineal surgery is reserved for cases in which repeated endoscopic procedures have failed or in which concomitant incontinence is another problem to be corrected. Endoscopic surgery seems to be the initial preferred treatment approach [3, 4]. Although these extensive and potentially morbid procedures are characterized by a low rate of stricture recurrence, they bear a high risk of urinary incontinence, thus the implantation of an artificial sphincter is often needed [5-7].

Table I.1.5.2.1 offers a summary of the various techniques described for the endoscopic management of post-RP VUASs.

Endoscopic modality	**Investigator**	**N**	**Follow-up (months)**	**S1 (%)**	**Sx (%)**	**Evidence level**
Dilation	Ramchandani, 1994	27	31.5	59	NR	3
	Geary, 1995	80		45.5		
	Thiel, 2006	43		100		
	Zhang, 2014	40		93		
	Park, 2001	26	12	NR	92.3	
DVIU	Surya, 1990	18		62		3
	Dalkin, 1996	17	14.5	88	100	3
	Borboroglu, 2000	52		58		3
TUR-AS	Popken, 1998	24		100		3
Ho:YAG laser	Hayashi, 2005	3		100		4

	Lagerveld, 2005	10	18	100	100	4
	Eltahawy, 2008	24	24	83	96	3
Endourethroplasty	Chiou, 1996	2	25	100	100	4
	Kuyumcuoglu, 2010	11		55		3

Table I.1.5.2.1: Endourologic treatment approaches of VUAS, adapted from SIU 2014 [5, 82].
N = Number of patients
S1 = Success after one treatment
Sx = Success after multiple treatments
NR = Not recorded
DVIU = Direction vision internal urethrotomy
Ho = Holmium
YAG = Yttrium-aluminum-garnet

In 2014, the Société International d’Urologie (SIU) consultation proposed stepwise treatment algorithms for both VUASs and postradiotherapy vesicourethral strictures (**Figures I.1.5.2.1 and I.1.5.2.2**). Even though these algorithms seem to be groundbreaking, they do not address the issue of how many transurethral manipulations should be tried before resorting to open reconstructive surgery. The reason is the limited data on the impact of repeated TUR-ASs on stricture recurrence and continence function in recurrent disease. In contrast, in bulbar urethral stricture there is clear evidence that recurrence rates rise up to 90% in the case of more than two direct vision internal urethrotomies (DVIU) [83]. Such data is lacking in patients with VUASs and would be of great interest, as the decision for open reconstructive procedures depends on the risk of stricture recurrence and incontinence of the various treatment options.

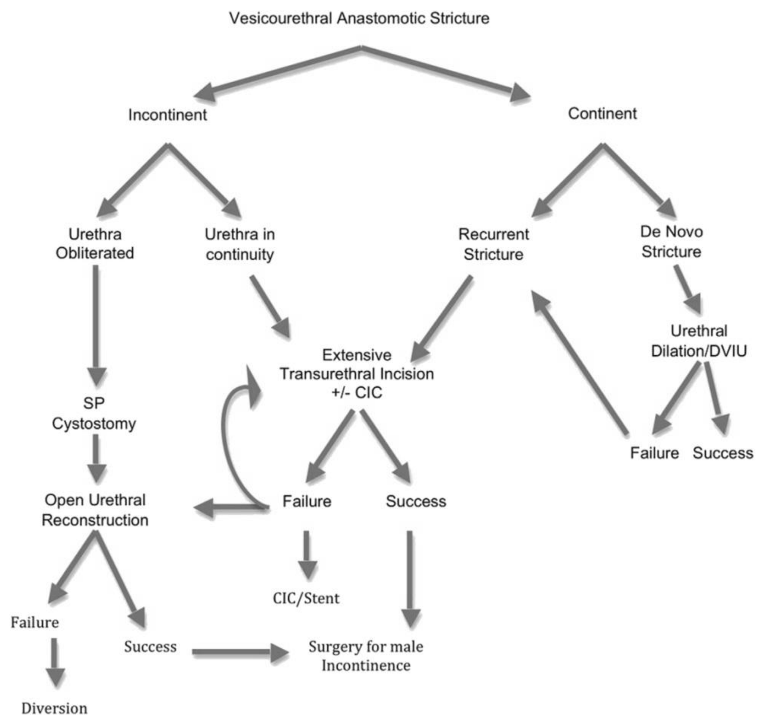


Figure I.1.5.2.1: SIU's proposed treatment algorithm for VUAS [5].
CIC = Clean intermittent catheterization
DVIU = Direct vision internal urethrotomy
SP = Suprapubic

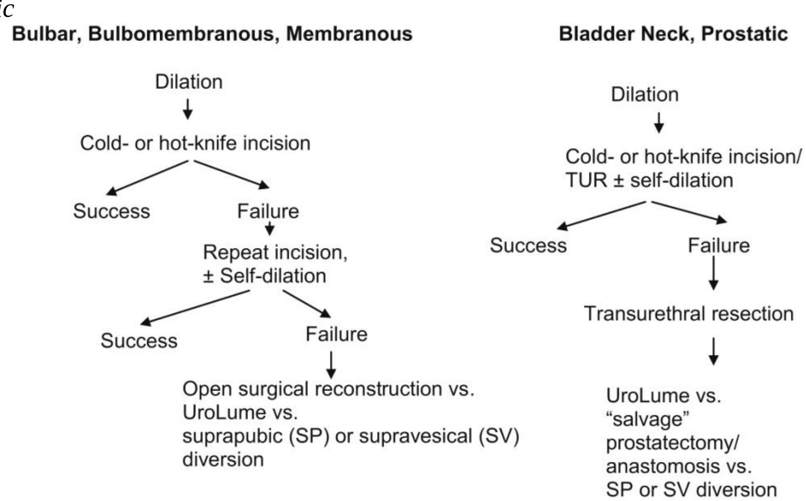


Figure I.1.5.2.2: SIU's proposed treatment algorithm for postradiotherapy (external beam radiotherapy, brachytherapy, combined modality) vesicourethral stenosis [5].

II. AIMS AND GOALS

Despite the well documented incidence and overall consensus that vesicourethral anastomotic strictures are one of the most common complications following radical prostatectomy, the management of anastomotic strictures seems to be controversial, resulting in difficulty in creating a unified treatment protocol, even though a series of different treatment strategies have been advocated in the literature and several improved operative techniques have been proposed and adopted by surgeons.

As a base for a clinically reasonable treatment algorithm it is of utmost importance to define the natural course of the disease and the success rates of the most frequently used therapeutic options.

The objective of this retrospective study is to investigate the natural history of patients, who suffered from recurrent VUASs and were treated by repeated TUR-ASs in a large tertiary center for reconstructive urology, with respect to:

- Defining the risk of stricture recurrence after every consecutive TUR-AS
- Time intervals between radical prostatectomy and occurrence of first stricture, as well as time intervals between recurrent strictures
- Patient characteristics (age, pre-existing conditions)
- Tumor characteristics (size, grading, Gleason score) and treat (radical prostatectomy approach, radiotherapy, castration therapy)
- Follow-up after radical prostatectomy (clinical follow-up and structured questionnaire assessing patient well-being and symptoms suggesting stricture occurrence)

III. MATERIALS AND METHODS

III.1. Study focus

Subjects for this retrospective study were men who were treated because of vesicourethral anastomotic stricture following radical prostatectomy (RP) and underwent transurethral resection of the anastomotic stricture (TUR-AS) in the University Hospital Munich, Großhadern. Patients' recruitment was based on electronic review of diagnostic database of the urology department and outpatient clinic. Criteria for review were men treated for VUASs after RP with TUR-AS in our urology department between February, 2005 and May, 2016, and who had a clinical follow-up of at least 12 months. Circumstances that lead to the diagnosis of VUAS were recorded. Concomitant clinical and oncological data related to prostate cancer were collected. As yet, no evidence-based recommended workup was available for new or persistent lower urinary tract symptoms (LUTS) after treatment of prostate cancer, therefore patients treated with TUR-AS were sent to a follow-up examination after three months or in case of earlier obstructive symptoms with post-void ultrasound and flow test at their office-based urologist. In case of obstructive symptoms or post-void residual volume, a urethroscopy was done. In case of stricture recurrence, the patients underwent repeated TUR-AS. Before performing a third TUR-AS, open reconstructive surgery was proposed. The number of recurrences of VUASs and time intervals between recurrences were recorded; alternative treatment strategies were also recorded. All the data at each of the first 6 TUR-AS were analyzed, including type of operation, pathological data and especially the time to a possible relapse.

All patients underwent a phone-based interview at the time of the record review and received a validated structured questionnaire (ICIQ - EORTC QLQ-C30).

Some patients underwent TUR-AS elsewhere. Others were lost to follow-up. All these patients were not included in the analysis. The study only included the men with VUAS(s), who underwent TUR-AS(s) in our department and outpatient clinic.

Transurethral resection of the anastomotic stricture was performed in the University Hospital Munich Großhadern, under general anesthesia. VUAS was confirmed preoperatively by voiding cystourethrography and / or cystoscopy, uroflowmetry and examination of residual urine. The urethra was accessed with a cold-knife urethrotomy. After visual confirmation of the typical aspect of a stricture of the vesicourethral anastomosis and after identification of the sphincter muscle, cold-knife incision was made in the 5 and 7 o'clock position to enable the surgeon to enter the bladder with the 26 Charrière resectoscope. Then a monopolar transurethral resection of the tough scar tissue was performed until soft or fatty tissue was reached. Resection was mainly done between 2 and 5 o'clock position and between 7 and 11 o'clock position to prevent rectal damage and symphysis fistula formation. The resected material was obtained for pathological evaluation. All patients were inserted a transurethral 24-Fr irrigation catheter postoperatively and the bladder was irrigated continuously with saline solution. The transurethral catheter was removed 2 days following the TUR-AS.

III.2. Study design

The study employed a retrospective design, using all the medical documentation available for each patient who satisfied the entry criteria and was eligible for inclusion in the study. Data that were collected regarding each case included:

- Date of birth
- Pre-existing conditions
- Tumour size, nodal state, grading, Gleason score and inital PSA (iPSA)
- Type and date of RP (RRP/RALP)
- Duration of post-RP catheterization
- Adjuvant radiotherapy
- Symptoms upon admission for TUR-AS
- Date of each TUR-AS
- Time intervals between TUR-AS
- Surgical report of each TUR-AS
- Report of pathology of each TUR-AS
- Duration of post-TUR-AS catheterization
- Use of analgesics
- Surgeon name

III.3. Study analysis

The statistical analysis was performed using Microsoft Excel 2016 und IBM Statistical Packet for Social Sciences (SPSS, version 24). The mean, maximum and minimum values of the parameters as well as the percentages of each category were calculated and some presented as diagrams. Chi-square test according to Pearson was performed to statistically evaluate a correlation between the intervals of stricture recurrence. Statistically, a value of p less than 0.05 was considered to be significant.

IV. RESULTS

IV.1. Descriptive statistics

The electronic review showed 86 men, of whom 60 men underwent at least one TUR-AS in the University Hospital Munich Großhadern, after RP, and were included in this study (**Table IV.1.1**). The mean patient age at the time of the RP was 64.7 years (IQR 81.4-48.6 years) and at the time of initial TUR-AS 65.5 years (IQR 81.7-48.8 years). RP had been performed in different institutions by either open retropubic or robot-assisted laparoscopic approach (96.7% and 3.3%, respectively). Patient underwent the initial TUR-AS after a mean of 10.5 months (IQR 1.2-98.5) after RP. All patients underwent TUR-AS as described above. Resected material was obtained for pathological evaluation in all cases. The evaluation revealed fibrosis and prostate cancer residual in 95% and 5% of patients, respectively. The median of recurrences of VUASs after initial TUR-AS was 1, with a maximum of 11 times.

Patient age at time of RP	Mean 64.7 years (IQR 81.4-48.6)
Open retropubic radical prostatectomy	96.7% (58 of 60)
Robot-assisted radical prostatectomy	3.3% (2 of 60)
Patient age at time of initial TUR-AS	Mean 65.5 years (IQR 81.7-48.8)
Time interval between RP and initial TUR-AS	Mean 10.5 months (IQR 1.2-98.5)

Table IV.1.1: Descriptive statistics of patient data.

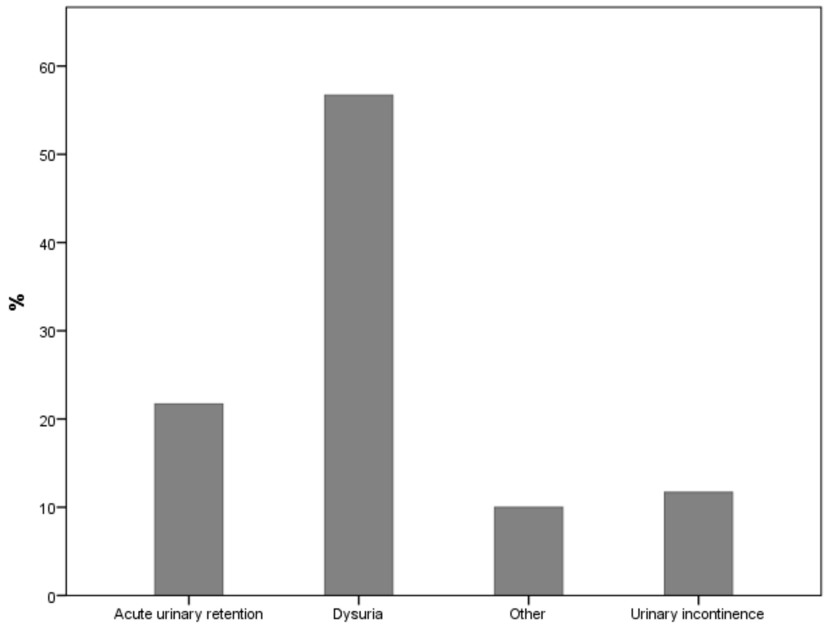
Patients' basic pathological data of prostate cancer are summarized in **Table IV.1.2**. 36.7% and 13% of patients had adjuvant radiotherapy and castration therapy between RP and diagnosis of VUAS, respectively. Patients who underwent adjuvant radiotherapy developed the first VUAS after a mean of 10.5 months after RP and their median of recurrences of VUASs after initial TUR-AS was 2.

At the time of the diagnosis of the initial VUAS, 18.3% of patients already had biochemical recurrence of prostate cancer.

iPSA (ng/ml)		25.6 (0.9-244)
pT-status	pT1	3.3% (2 of 60)
	pT2	46.7% (28 of 60)
	pT3	48.3% (29 of 60)
	pT4	1.7% (1 of 60)
Lymph node status	pN+	23.3% (14 of 60)
	pN-	76.7% (46 of 60)
Gleason score	≤6	20% (12 of 60)
	7	38.3% (23 of 60)
	8	18.3% (11 of 60)
	9/10	23.3% (14 of 60)
Surgical margin	Positive	40% (24 of 60)
	Negative	60% (36 of 60)
Postoperative radiotherapy	Yes	36.7% (22 of 60)
	No	63.3% (38 of 60)
Castration therapy	Yes	13.3% (8 of 60)
	No	86.7% (52 of 60)

Table IV.1.2: Patients' basic pathological data of prostate cancer.

The symptoms leading to the diagnosis of initial VUAS were dysuria (56.7%), acute urinary retention (21.7%), urinary incontinence (11.7%) or other unspecific complaints (10%), as presented in **Graph IV.1.1**.



Graph IV.1.1: Symptoms leading to diagnosis of VUAS.

IV.2. Statistical analysis

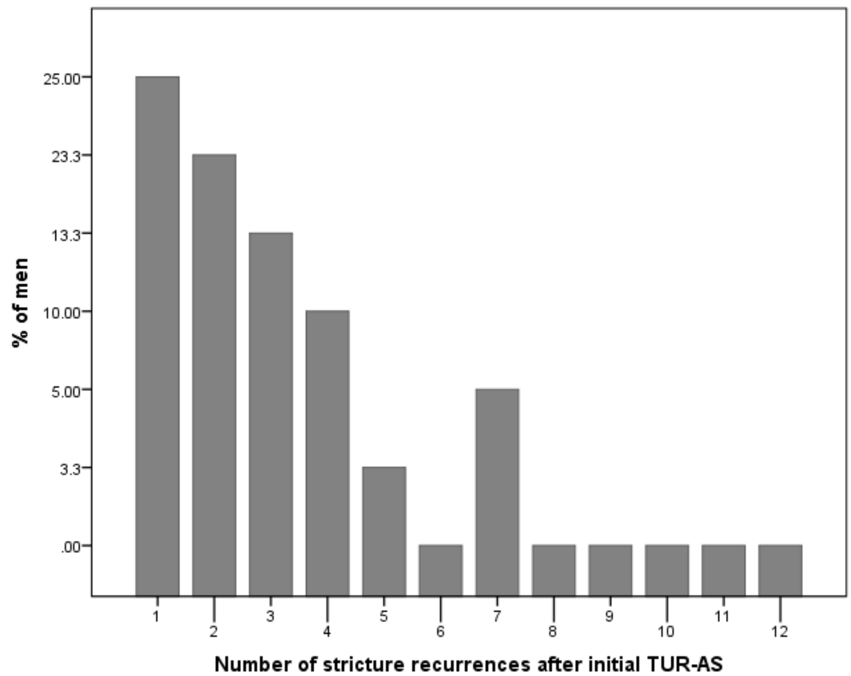
The mean postoperative follow-up time was 36.1 (IQR 12-72.6) months. 73.3% of patients had recurrence of VUAS after initial TUR-AS and a repeated TUR-AS was performed in these patients. The mean time interval to recurrence of VUAS after initial TUR-AS was 8.2 (IQR 0.3-51) months.

61.3-75% of patients had recurrent VUAS after every consecutive TUR-AS (**Table IV.2.2**). 75% of patients were stable after one or more TUR-AS (**Table IV.2.1**). 21.7% of patients underwent open surgery for either ileal conduit procedure or perineal re-anastomosis and artificial sphincter placement. 6.7% and 3.3% of patients required repeated dilation and suprapubic catheter placement, respectively. 5% of patients received a steroids injection in at least one of the procedures, and had a median of 6 recurrences of VUAS after initial TUR-AS. 61% of the patients, who underwent open reconstructive surgery, were patients who underwent adjuvant radiotherapy or castration therapy. In patients who did not undergo open surgery, there was a mean use of 2.2 (IQR 0-10) pads/day at the last follow-up.

Recurrence of VUAS after initial TUR-AS	73.3% (44 of 60)
Stable after one or more TUR-AS	75% (45 of 60)
Urinary diversion	11.7% (7 of 60)
Perineal re-anastomosis and artificial sphincter	3.3% (2 of 60)
Repeated dilation	6.7% (4 of 60)
Suprapubic catheter	3.3% (2 of 60)

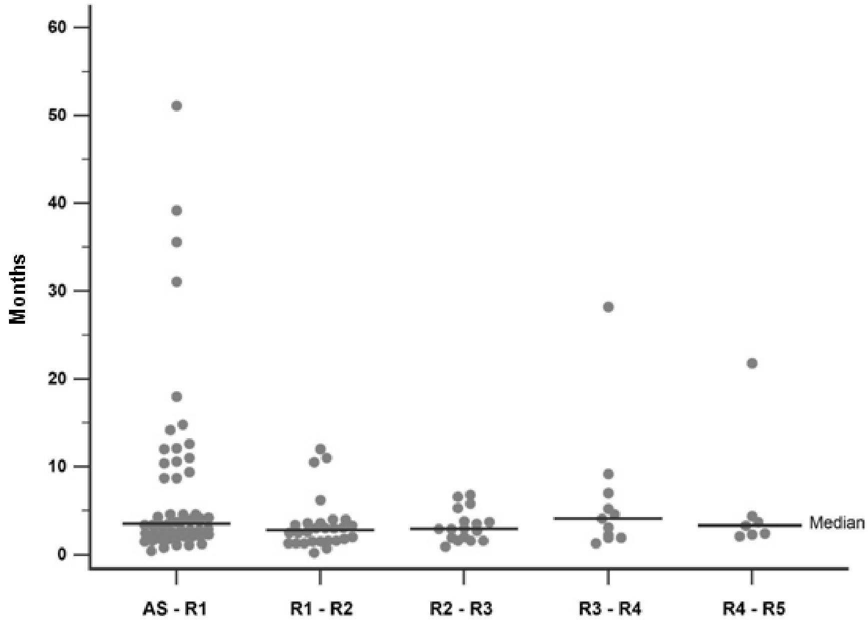
Table IV.2.1: Status of patients after TUR-AS.

Graph IV.2.1 shows the percentage of patients according to the number of VUAS recurrences after the initial TUR-AS.



Graph IV.2.1: Percentage of patients according to the number of recurrences after the initial TUR-AS.

Graph IV.2.2 demonstrates the number of patients at each recurrence of VUAS as well as the time interval between each recurrence episode.



Graph IV.2.2: Number of patients at each recurrence of VUAS as well as the time interval between each recurrence episode.
AS = Initial VUAS; R = Recurrence of VUAS*

The mean time intervals between each episode of TUR-AS are summarized in **Table IV.2.2**. The mean time between TUR-AS intervals after initial TUR-AS was 5.2 months.

Interval	rPX - S1	S1 - R1	R1 - R2	R2 - R3	R3 - R4	R4 - R5
Mean time (months)	10.5 (1.2-98.5)	8.2 (0.3-51)	3.3 (0.02-12)	3.6 (0.02-6.7)	6 (0.01-28.2)	4.8 (1.9-21.8)
% of patients with R	100% (60 of 60)	73.3% (44 of 60)	45% (27 of 60)	30% (18 of 60)	20% (12 of 60)	15% (9 of 60)
Recurrence rate preceding TUR-AS	-	73.3% (44 of 60)	61.3% (27 of 44)	66.7% (18 of 27)	66.7% (12 of 18)	75% (9 of 12)

Table IV.2.2: Mean time intervals between each TUR-A, percentage of patients with recurrence of VUAS of total number of patient collective, and recurrence rate at each recurrence episode after initial TUR-AS.
rPX = Radical prostatectomy; S1 = Initial VUAS after rPX; R* = Recurrence of VUAS

V. DISCUSSION

Although the precise treatment of VUASs and their recurrences after RP is still unclear, globally, several hypotheses have been proposed and investigated. This retrospective study reviewed the epidemiology, etiology, pathophysiology and various treatment options, with the objective of investigating the natural history of VUASs after RP.

The mean time interval between RP and first VUAS formation was discovered to be 10.5 months, with or without adjuvant radiotherapy (**Table IV.1.1**). Studies have observed and documented the occurrence of VUAS after RP within 2 years, with 66% of VUASs appearing within 6 months after surgery [1]. Dysuria was found to be the most common symptomatic presentation of VUAS. Although the mean time interval to symptoms' onset after RP seems to be 10.5 months, patients might have had urinary discomfort long before presenting in our hospital, and maybe did not report their symptoms due to shame or fear of social stigma. Due to the facts that more than two thirds (73.3%) of patients suffered from recurrence after the initial TUR-AS (**Table IV.2.1**) and a mean use of 2.2 pads/day was recorded, both a high risk of recurrence after initial TUR-AS and a significant impact on patients' quality of life were observed. The mean 36.1 months structured postoperative follow-up time showed that 15% of the patients underwent at least a fifth TUR-AS after the initial TUR-AS.

These findings are in contrast to some data in current literature: Multiple studies investigating various treatment techniques such as dilation, laser incisions, cold- or hot-knife incisions, incisions or dilations with steroids or Mitomycin injection, and TUR-AS have shown high success rates. Nonetheless, these series had a short observation time, the success rates reported was not sufficiently defined, and many of the subjects required further interventions (**Table I.1.5.2.1**).

Although urethral dilation has been favoured in early (less than 6 weeks after RP) VUAS, its success rates have varied. Ramchandani et al. [84] used a transurethral balloon dilation technique and reported a 59% success rate at a mean follow-up time of 31.5 months. In 2001, Park et al. [8] reported a 92.3% success rate in 26 patients by using a Nottingham catheter passed over a guide cystoscopically; however, 7 of these patients underwent more than one dilation, and the mean time interval between dilation episodes was 2.75 months. In contrast to these reports, the mean time interval between TUR-AS intervention episodes after initial TUR-AS in this study was much longer at 5.2 months, and although 6.7% of the patients required repeated dilation, a stricture-free status was achieved.

Contrary to LaBossiere et al. [85], who reported a pattern of significantly higher success rates with first (69%) or second (58%) treatments compared with a third (38%) or more (32%) treatments in a study of holmium laser incisions in 142 patients, recurrence rates in this study varied between 61.3% and 75% without any sign of significant pattern of recurrence (**Table IV.2.2**). Cold- or hot-knife incisions have also been used to treat VUAS with comparable outcomes to holmium laser incision in many series. Although Ramirez et al. [86] reported a 72% success rate at a mean 13 months of follow-up, 80% of the patients suffered from stress urinary incontinence and 65% of these patients underwent surgical reconstruction. In comparison, only 21.7% of the patients in this study required surgical reconstruction.

The injection of steroids at the incision sites is thought to potentially prevent recurrent scar formation by enhancing endogenous collagenase and thus reduce contracture. Eltahawy et al. [87] published in 2008 a series of 24 patients who underwent holmium laser incisions followed by injection of triamcinolone at the incision sites, and reported a 83% success rate with 70% requiring one treatment and the remainder requiring a second incision and injection at 6 weeks. In comparison, the %5 of patients in this study who underwent at least one TUR-AS with steroids injection had a median of 6 VUAS recurrences, 66.7% of them required at least a fifth TUR-AS, and the remainder a third TUR-AS after the initial intervention. These findings contradict the hypothesis that TUR-AS with steroids injection reduces VUAS recurrences, since the patients who did not receive steroids injection had a median of 1 VUAS recurrences.

In 2013, Kravchick et al. [88] reported three different treatment modalities in a collective of 32 patients; urethral dilation succeeded in only 3 (10.3%) patients, urethral dilation with consecutive transrectal ultrasonography-guided injection of steroids in the scar area showed a 93% success rate in 14 patients, and TUR-AS was performed in 7 patients, who did not need re-treatment, had however, the highest incontinence rates (57.1%). In contrast, patients in this study who required interventions complained mainly of dysuria rather than urinary incontinence **(Graph IV.1.1)**.

Lagerveld et al. [89] reported in 2004 a 100% success rate of recurrent and resistant VUAS in 10 patients by transurethral resection using holmium laser by creating a deep incision of the scar tissue at the 6 o’clock position and vaporizing resection of the remaining scar tissue between 3 and 9 o’clock. While this approach might seem promising, the mean follow-up of 18 months reported was insufficiently structured and success was not adequately defined, as preexisting irritative voiding complaints and incontinence did not change after treatment.

In current literature, the only reported study, which investigated TUR-AS as a treatment modality for VUAS after RP, was published by Popken et al. [4] in 1998, who retrospectively reviewed 340 patients, who underwent circular transurethral resection with 24F resectoscope or transurethral cold knife incision at 0, 120 and 240° of the scar tissue at the site of vesicourethral anastomosis after RP between 1988 and 1996, and reported a 100% success rate. The catheter was removed after a mean of 13.1 days, with an incidence of 9% of acute urinary retention. Nonetheless there was no structured follow-up investigation to rule out recurrence reliably.

Alternative procedures that have been proposed include robotic bladder neck reconstruction, which however have been associated with a recurrence rate of 25% and an incontinence rate of 82% [90].

The most severe VUAS require an aggressive reconstructive approach. Temporary suprapubic drainage will allow planning for reconstruction or diversion. Only in selected patients, suprapubic drainage might be the best long-term treatment strategy, as in 3.3% of patients in this study.

Before a third TUR-AS was performed, an open reconstructive surgery was proposed and performed in 21.7% of the patients. It is essential to mention, that 61% of the patients, who underwent open reconstructive surgery, were patients who underwent adjuvant radiotherapy or castration therapy. Radiotherapy has been vastly documented as a risk factor for the development of TUR-AS and its recurrence, due to secondary chronic fibrosis formation and progressive endarteritis with eventual tissue scarring [84]. Nevertheless, it is imperative to investigate the delayed urinary adverse effects of radiotherapy, because of high prevalence of patients living long term after radiotherapy and the accumulation of adverse effects over an extended time horizon.

Although the recurrence rates of VUAS after initial TUR-AS varied between 61.3% and 75%, a stricture-free status could be achieved, with 75% of patients being stable after one or more TUR-AS (**Table IV.2.1** and **Table IV.2.2**). In contrast, repetitive dilations and urethrotomies of urethral strictures have shown low success rates of 9% after 3 years of follow-up, and a nearly 0% chance of being stricture-free at 4 years [91]. Albers et al. [92] retrospectively analysed 937 patients with strictures who underwent internal urethrotomy with a mean follow-up of 4.6 years, and reported that if a stricture has undergone three or more urethrotomies, the chance of lasting success approaches zero, and therefore reconstructive surgery should be considered in patients at high risk for stricture recurrence and with more than one treatment failure.

The SIU suggests that in case of failed stricture dilation or occurrence of stricture after 6 weeks after RP, a stepwise approach with the goal of preserving urinary continence should be advocated (**Figure I.1.5.2.1**) [84]. However, no study exists in current literature which has sufficiently investigated the recurrences of VUAS with a proper follow-up. The American Urology Association (AUA) guidelines for male urethral stricture state that a dilation, vesicourethral incision or transurethral resection for post-RP VUASs with evidence strength grade C is recommended [93]. In the events of an unsuccessful transurethral procedure, the AUA guidelines recommend an open reconstruction of the VUAS. However, open reconstructive surgery is associated with a very high risk of incontinence, and the decision of whether to offer this option to the patient is still not clearly defined, should be discussed and suited individually, since a chance of a stricture-free state exists [93].

In the University Hospital Munich Großhadern, the therapeutic option of transurethral resection and incision of the anastomosis is used depending on the severity of the stricture, if a surgical intervention is needed. Various methods and approaches have been documented for managing a VUAS, including electrocautery incision or resection, simple or balloon dilation, cold knife incision and laser treatment.

Most studies in the literature reported investigating a small number of subjects with a VUAS following RP. This study with a large number of 60 patients demonstrated that although initial TUR-AS is associated with a risk of recurrences, a stricture-free status could be achieved.

This study was limited to the retrospective design and did not have sufficient information regarding further TUR-AS treatments, intraoperative blood loss, extravasation of urine after RP, or patients' lifestyle.

VI. CONCLUSIONS

This retrospective single-centre analysis was made to investigate the natural history of anastomotic strictures following radical prostatectomy. Statistical analysis of several parameters in this study with a large number of patients showed that although TUR-AS is associated with a high recurrence rate, a stricture-free status could be achieved. Therefore, careful treatment selection is required, and the decision of whether to offer transurethral treatment or high risk associated open reconstructive surgery to the patient should be suited individually.

Further studies and follow-ups on patients with recurrent VUASs after RP are needed to better understand the precise course of this complication and to achieve sufficient treatment.

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VIII. AFFIDAVIT

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Eidesstattliche Versicherung

Khury, Farouk____

Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Natural history of post-prostatectomy vesicourethral anastomotic strictures treated by transurethral resection

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Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Ulm, 06.08.2022

Ort, Datum Farouk Khury

IX. LIST OF PUBLICATIONS

Can we define reliable risk factors for anastomotic strictures following radical prostatectomy?

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