# CENTER FOR RECONSTRUCTIVE URETHRAL SURGERY


**GUIDO BARBAGLI, M.D.**

**Arezzo - Italy**

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# My Journey Around the Urethra

## Past, Present and Future


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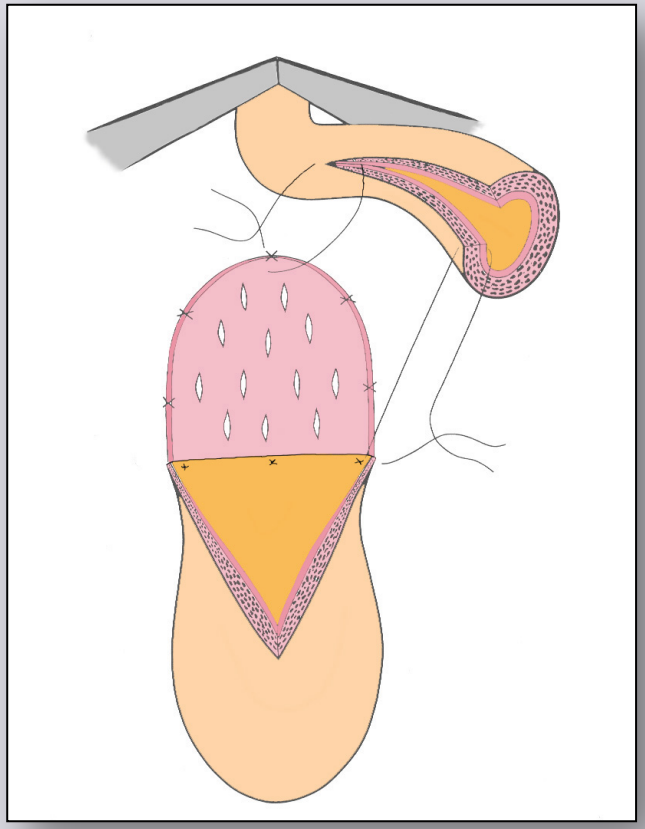
# My Journey Around the Urethra

## The Past:
## History of the dorsal skin graft urethroplasty



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# Clinical case history

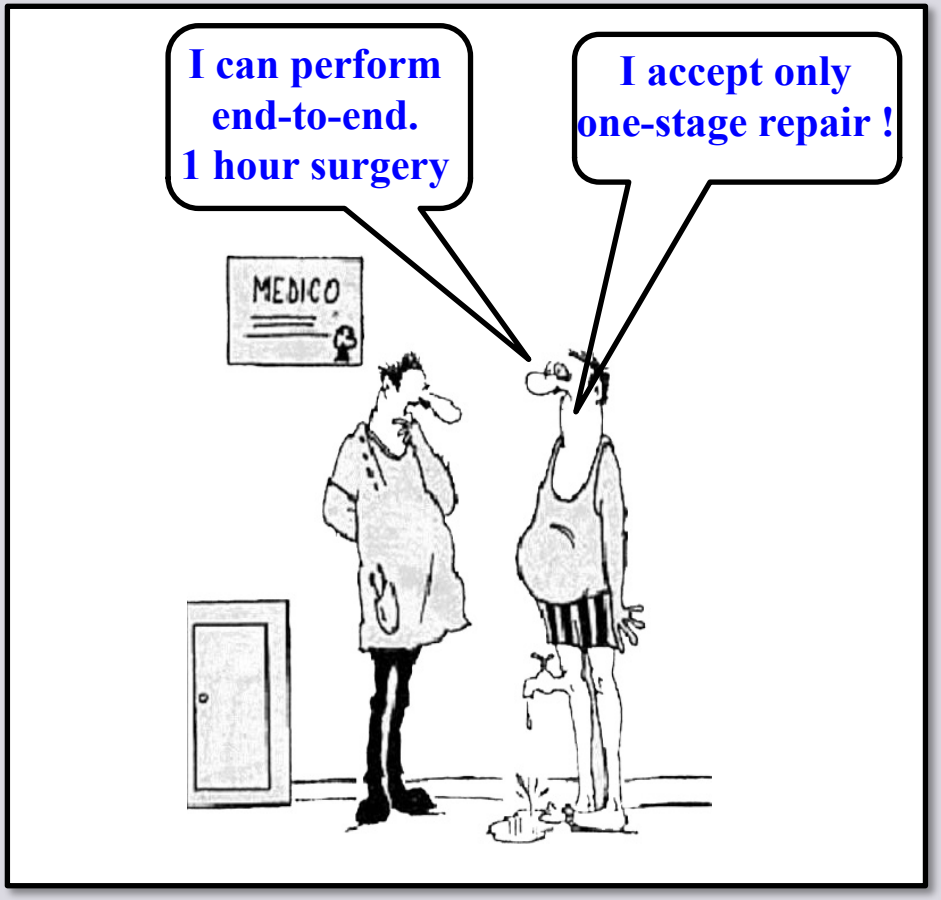
**Age 49 years old – uncircumcised – married - 2 children – no co-morbidities.**

**Blenorragia 20 years before.**
**Periodic dilations.**
**1987: internal urethrotomy.**
**1988: two-stage urethroplasty.**
**1989-1990: 3 internal urethrotomies.**

**Recurrent urinary tract infection, poor stream and post-voiding dribbling.**


**Uroflowmetry: Qmx 4 ml/sec**

**Ultrasonography: > 220 cc residual urine**

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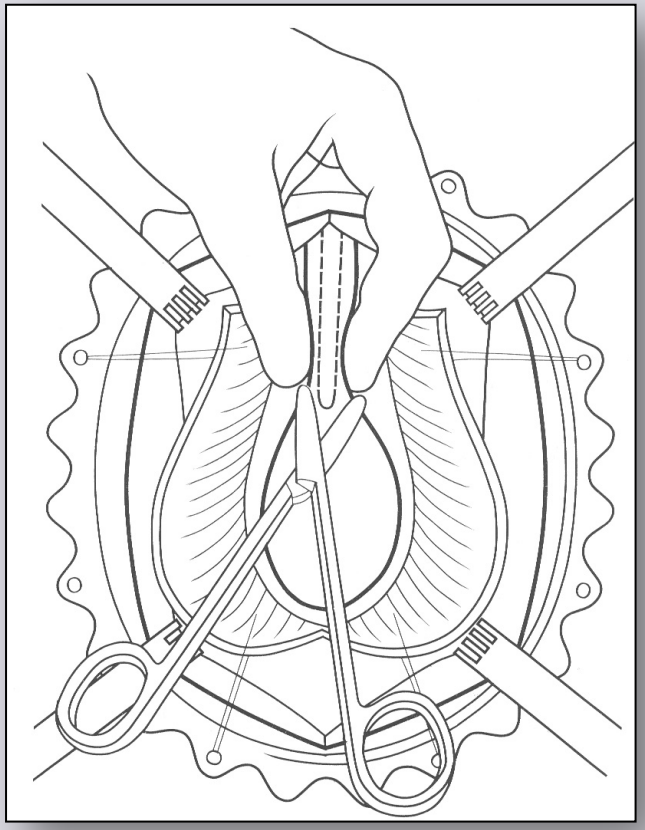
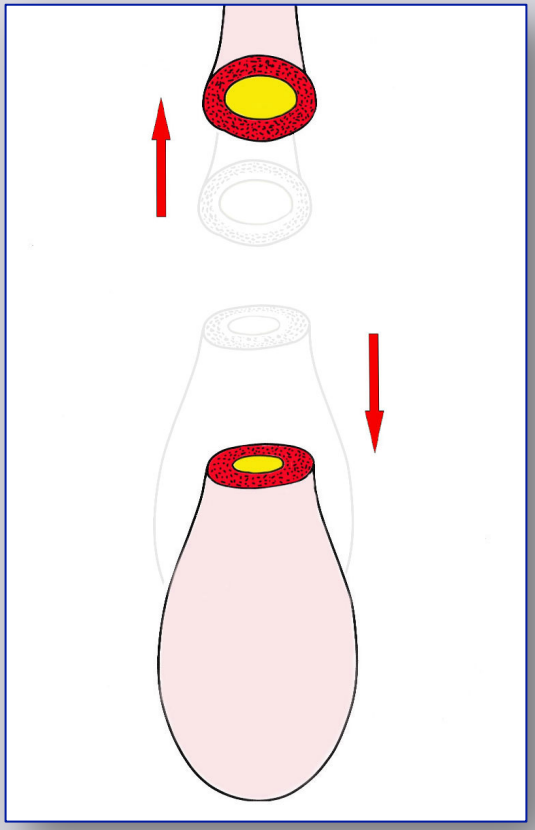
# Clinical case history: the surgery





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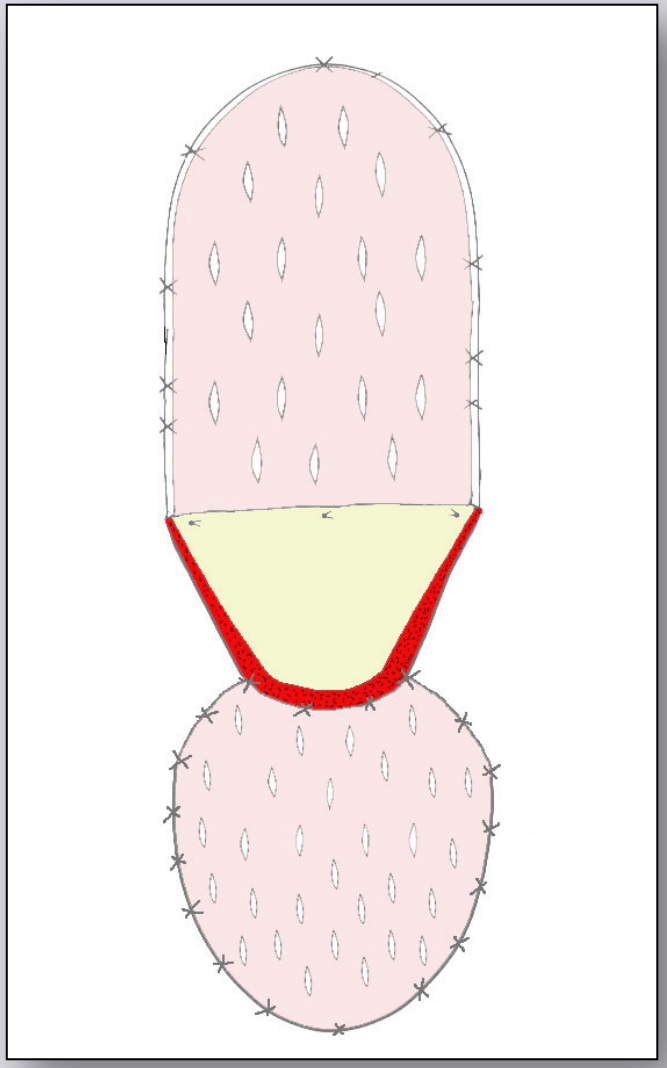
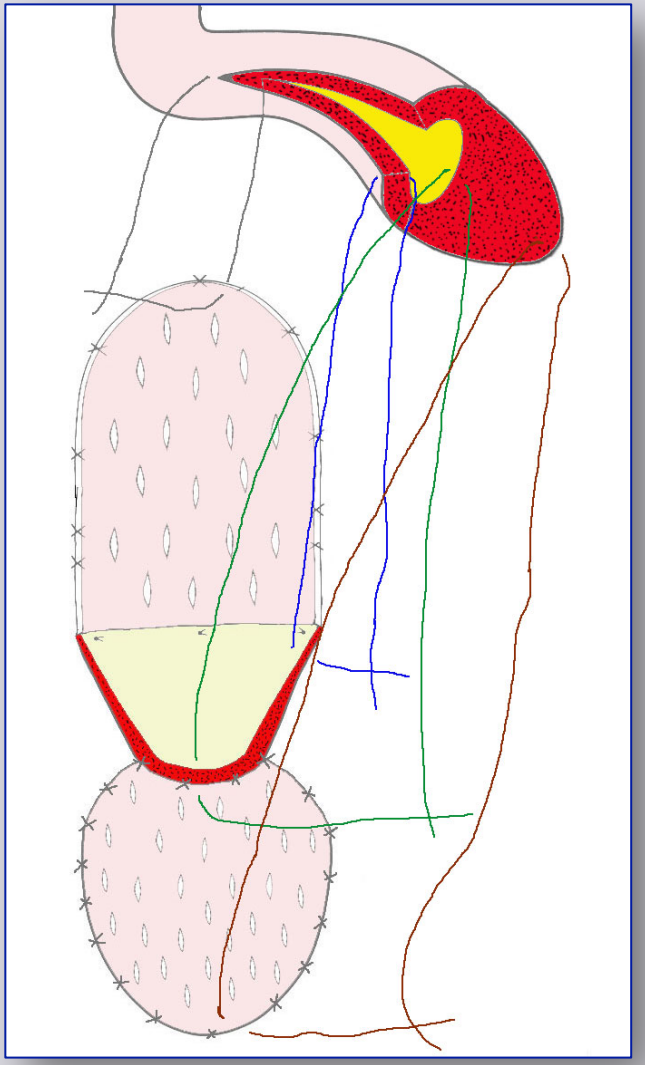
# Clinical case history: the surgery





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# Voiding cysto-urethrography

One month later

24 years later

**1990-2014: Uroflowmetry: Mean Qmx 25 ml/sec (range 15 – 36)**

DORSAL FREE GRAFT URETHROPLASTY

GUIDO BARBAGLI, CESARE SELLI, ALDO TOSTO AND ENZO PALMINTERI

*From the Department of Urology, University of Florence, Florence, Italy*

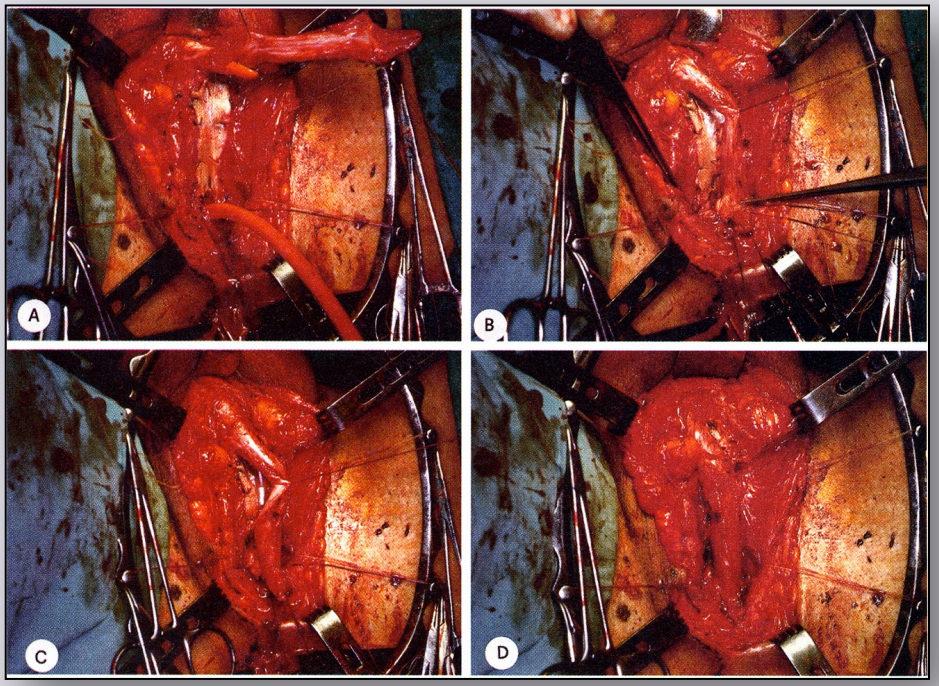
J Urol 1996; 155: 123-126

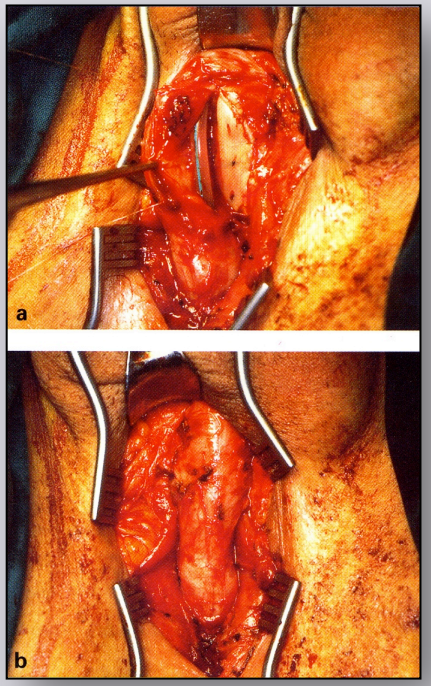
# A one-stage dorsal free-graft urethroplasty for bulbar urethral strictures

G. BARBAGLI, C. SELLI, V. di CELLO and A. MOTTOLA

*Department of Urology, University of Florence, Florence, Italy*

Br J Urol 1996; 78: 929-932



Christophe E. Iselin · George D. Webster

World J Urol 1998; 16: 181-185

# Dorsal onlay urethroplasty for urethral stricture repair

# DORSAL ONLAY GRAFT URETHROPLASTY FOR REPAIR OF BULBAR URETHRAL STRICTURE

J Urol 1999; 161: 851-818

CHRISTOPHE E. ISELIN* AND GEORGE D. WEBSTER

*From the Division of Urologic Surgery, Department of Surgery, Duke University Medical Center, Durham, North Carolina*

**G. D. Webster**

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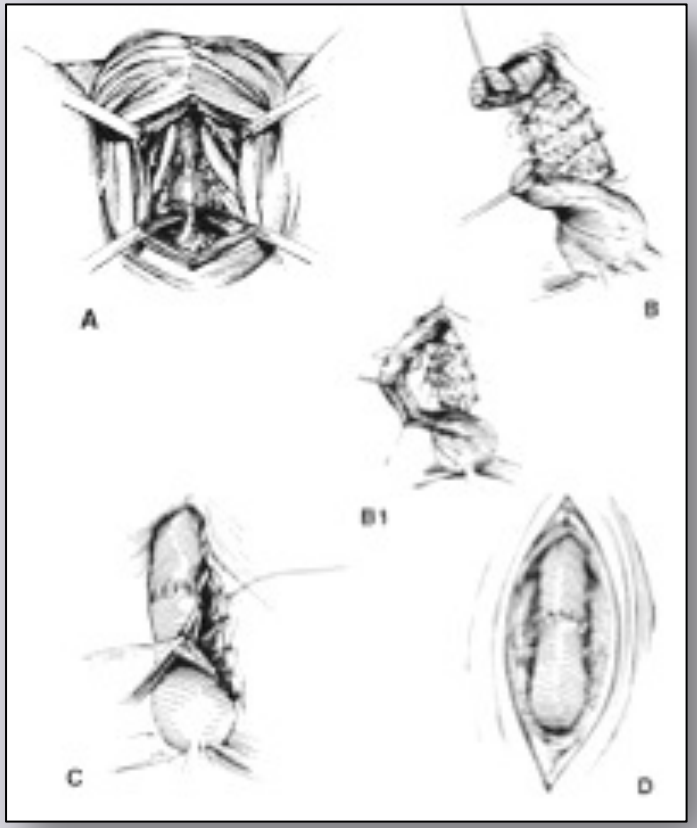
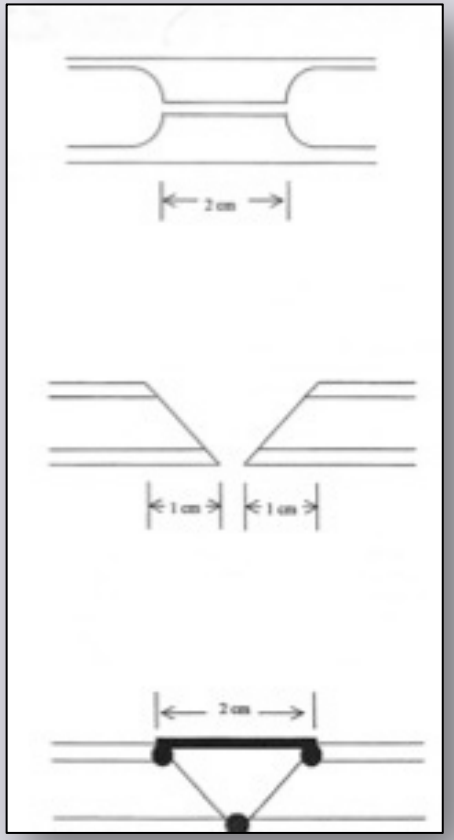
# THE AUGMENTED ANASTOMOTIC URETHROPLASTY: INDICATIONS AND OUTCOME IN 29 PATIENTS

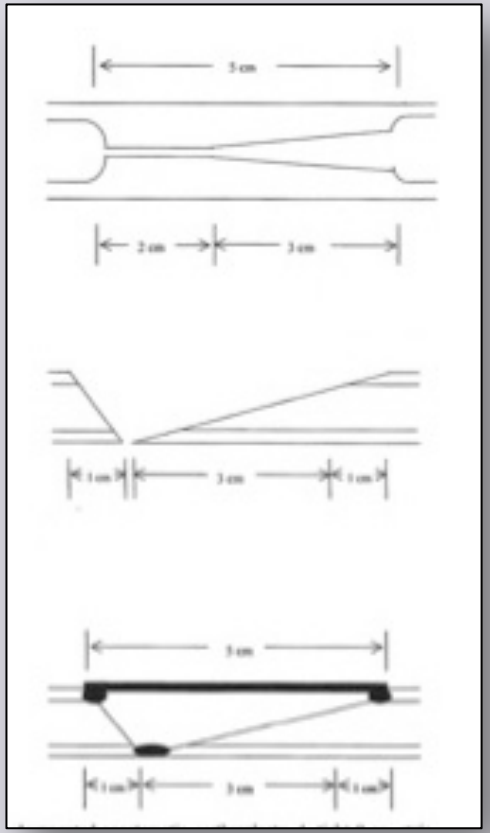
MICHAEL L. GURALNICK* AND GEORGE D. WEBSTER

*From the Division of Urologic Surgery, Duke University Medical Center, Durham, North Carolina*

**J Urol 2001; 165: 1496-1501**

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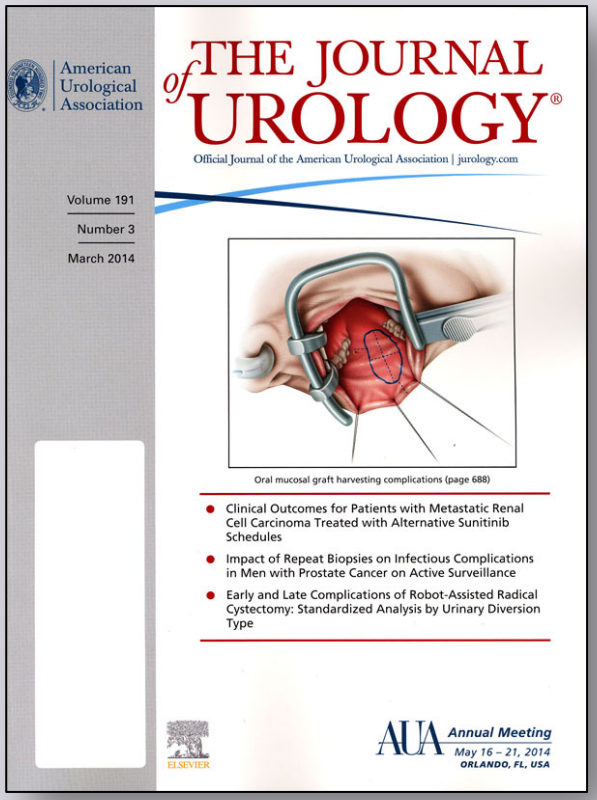
# My Journey Around the Urethra

## The Present:

## Evolution of the dorsal skin graft urethroplasty using oral mucosa

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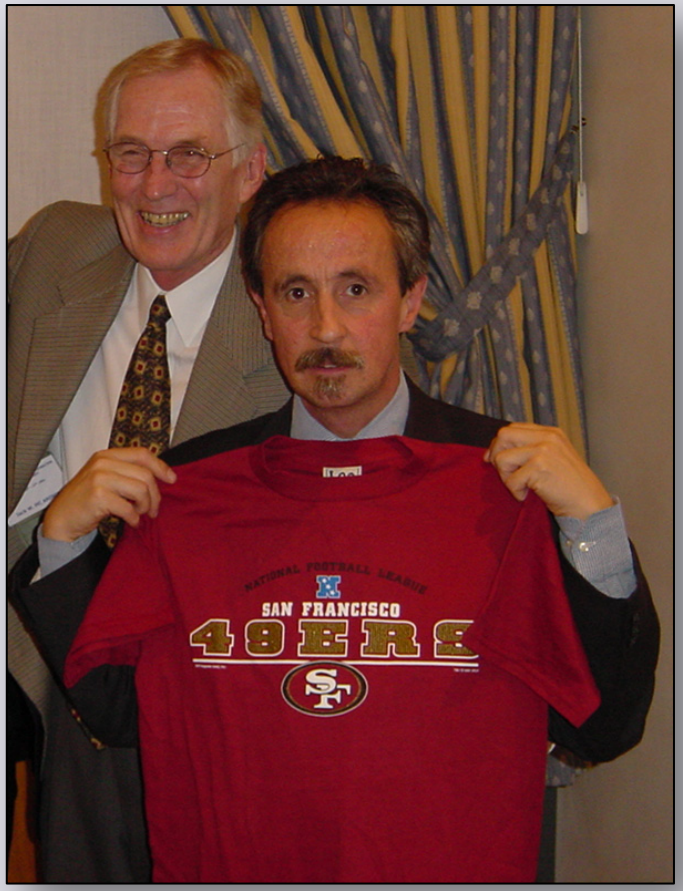


**Jack W. McAninch**

**Laurence S. Baskin**

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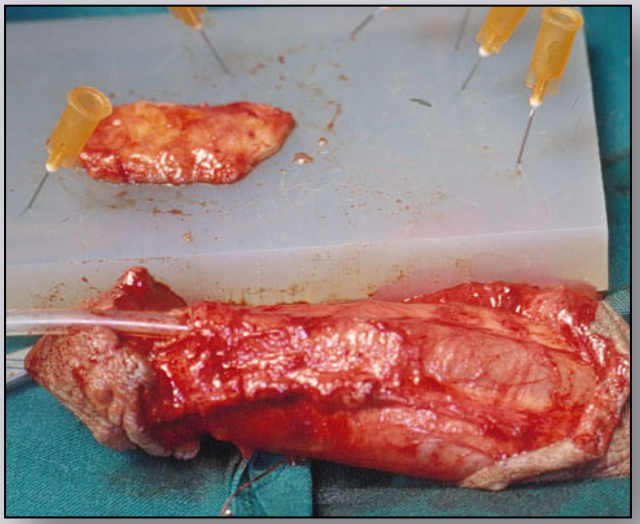

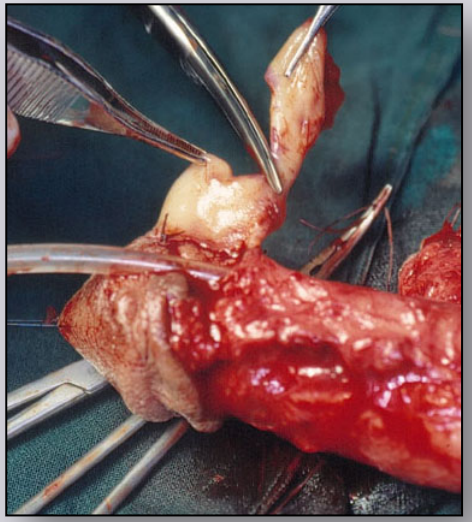

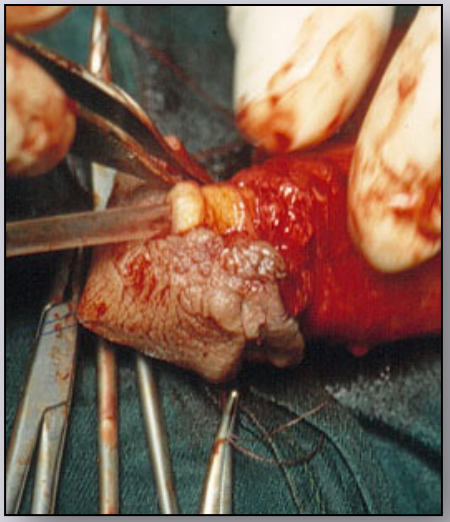

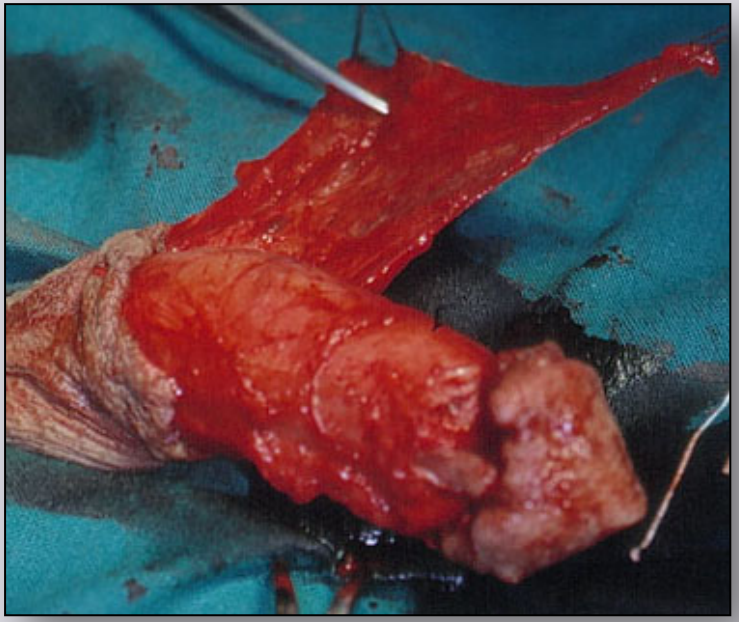

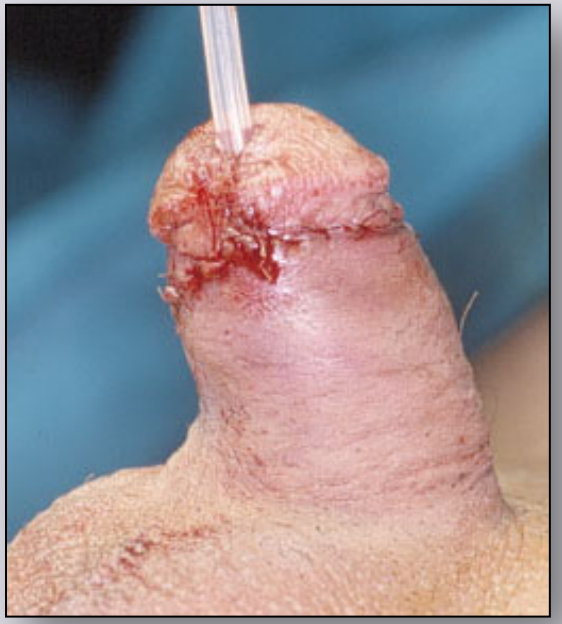

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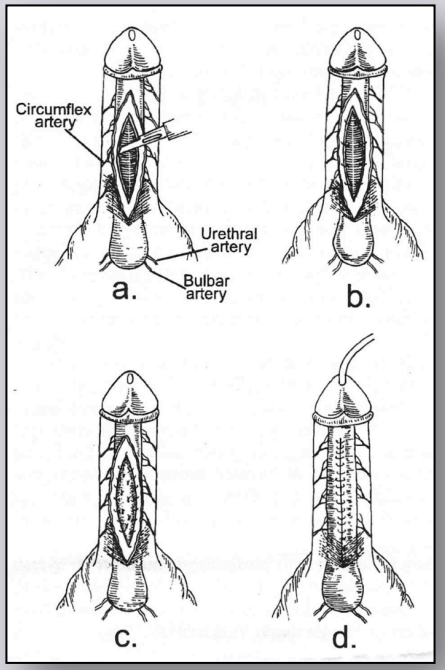
# DORSAL FREE GRAFT URETHROPLASTY FOR URETHRAL STRICTURE BY VENTRAL SAGITTAL URETHROTOMY APPROACH

HARI S. ASOPA, MUKUL GARG, GOVIND G. SINGHAL, LAKHAN SINGH, JYOTI ASOPA, AND ARCHANA NISCHAL

**Urology 2001, 58: 657-659**


**Hari S. Asopa**

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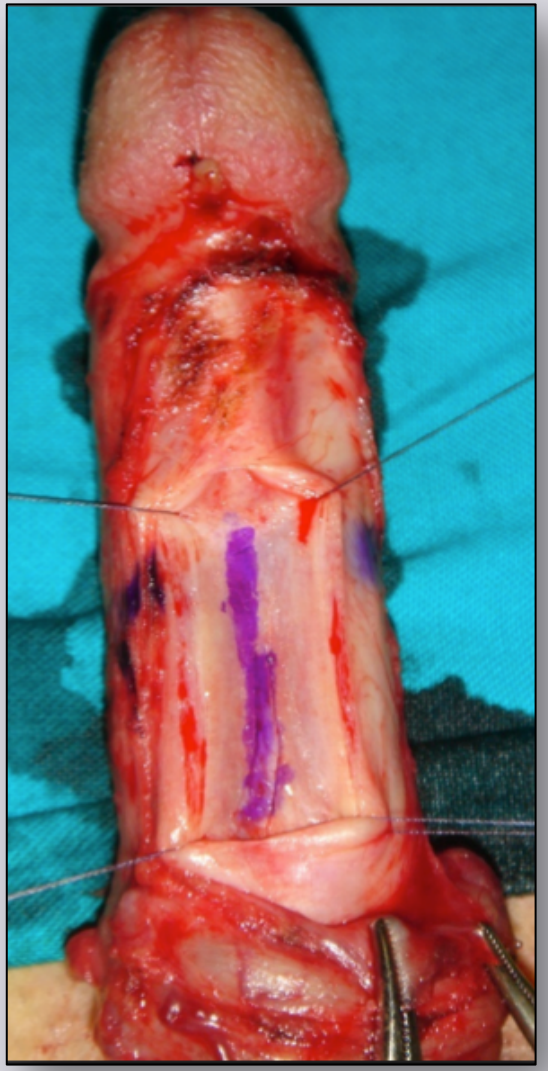
# Asopa's graft inlay technique



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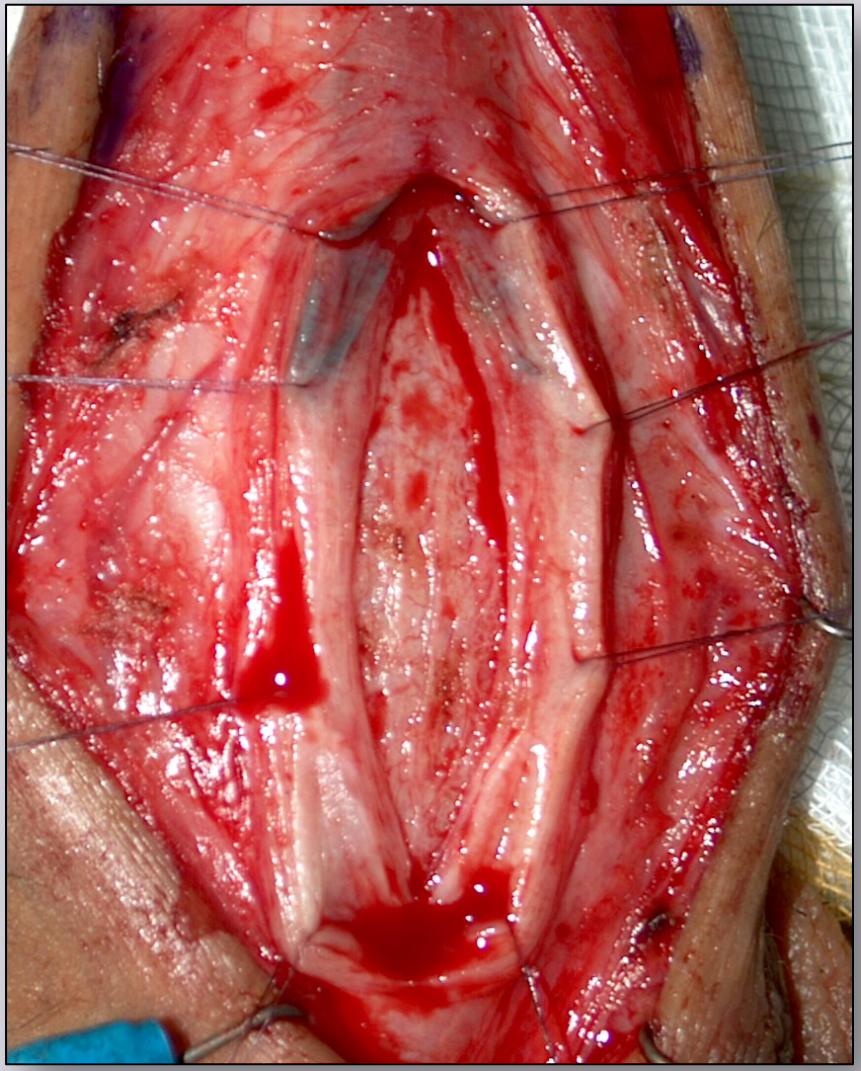
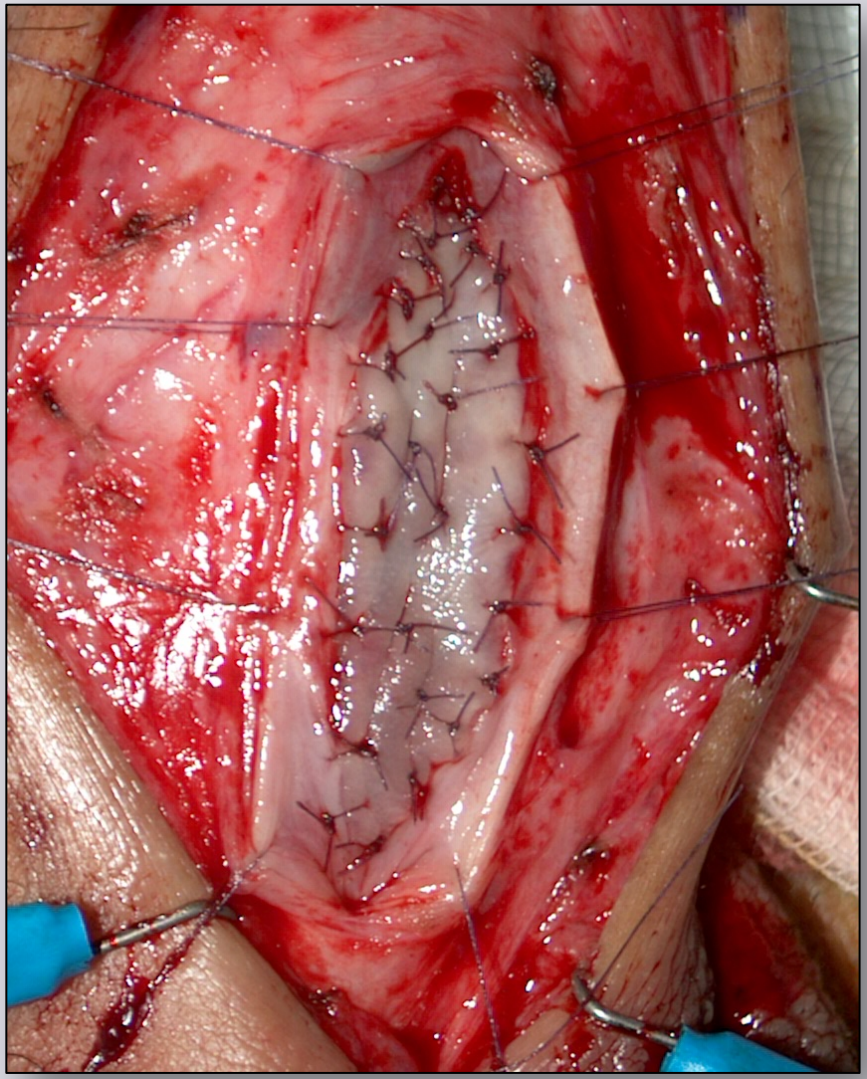
# Asopa's graft inlay technique





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# Asopa's graft inlay technique

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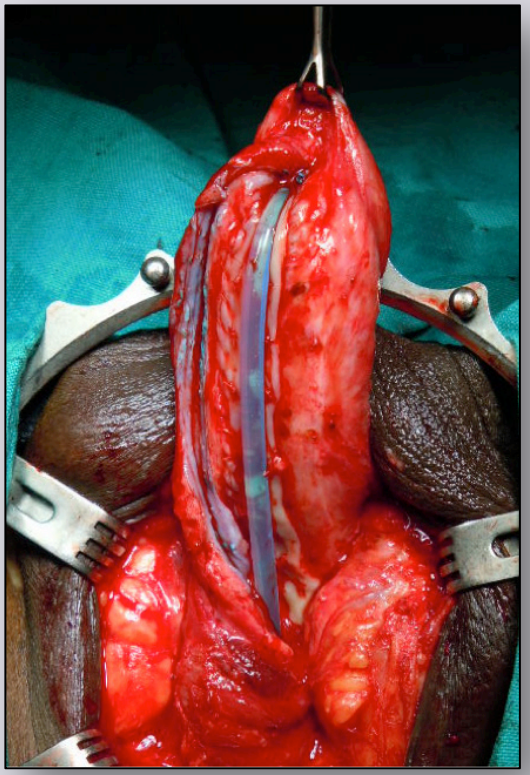
V31

**A NEW TECHNIQUE OF URETHROPLASTY FOR BALANITIS XEROTICA OBLITERANS.** *Sanjay B. Kulkarni, Jyotsna S. Kulkarni, Deepak V. Kirpekar.* Pune, India. (Presented by Sanjay B. Kulkarni)

INTRODUCTION AND OBJECTIVES: Balanitis Xerotica Oblilterans (BXO) is a common cause of urethral stricture. In past use of genital skin resulted in restenosis, requiring repeat operations. We wish to demonstrate a new technique of Single stage repair using Buccal Mucosa Graft (BMG) as Dorsal Onlay Graft (DOG) for the penile and bulbar urethra through perineal incision only.

**J Urol 2000, 163(4): 352 (abst. V31)**

**Sanjay B. Kulkarni**

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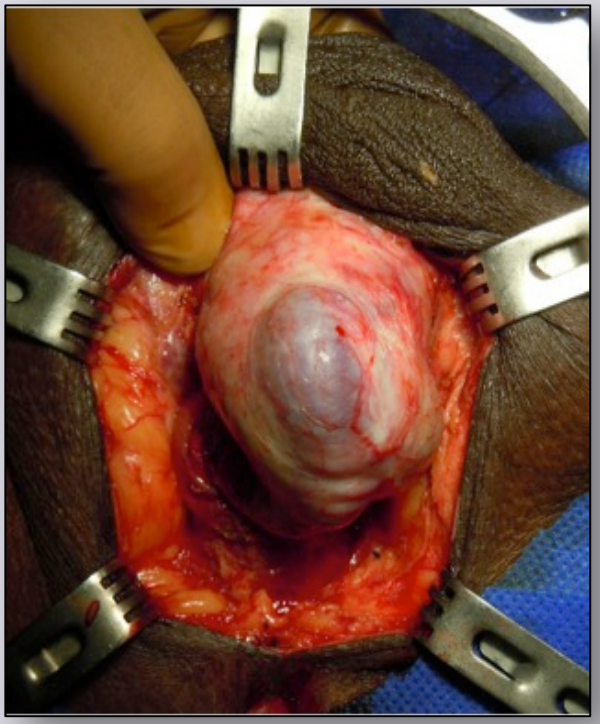
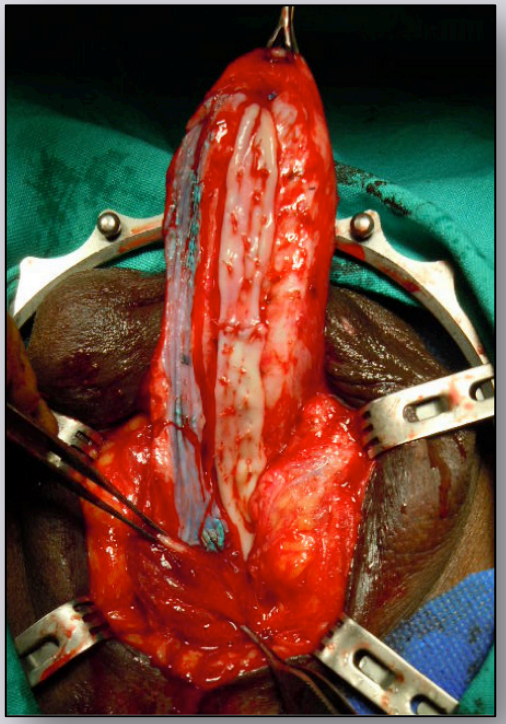
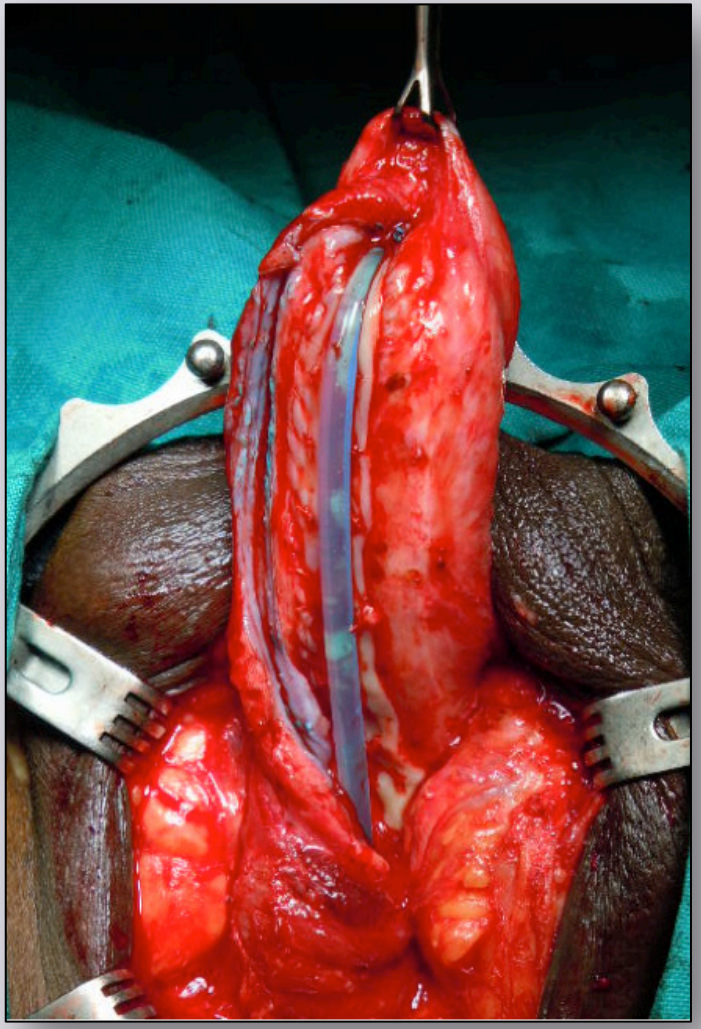
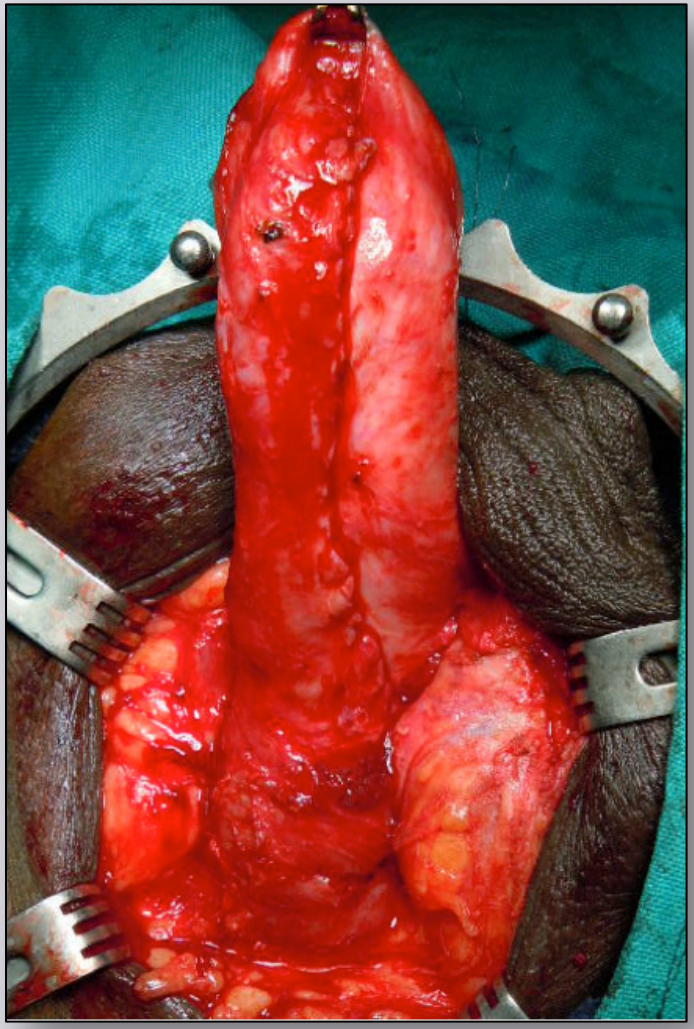
# Kulkarni's panurethroplasty by perineal approach





# Kulkarni's panurethroplasty by perineal approach





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BJUI

BJU INTERNATIONAL

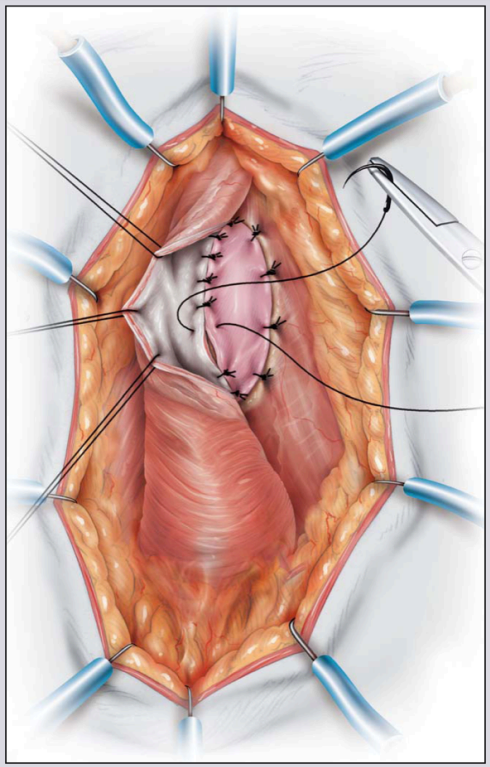
# One-sided anterior urethroplasty: a new dorsal onlay graft technique

Sanjay Kulkarni, Guido Barbagli*, Salvatore Sansalone† and Massimo Lazzeri†

*Centre for Reconstructive Urethral Surgery, Pune, India; *Centre for Reconstructive Urethral Surgery, Arezzo, †Department of Urology, University Tor Vergata, Rome, and †Department of Urology, Santa Chiara-Firenze, GIOMI Group, Florence, Italy*

**BJU Int 2009, 104: 1150-1155**

**Sanjay B. Kulkarni**

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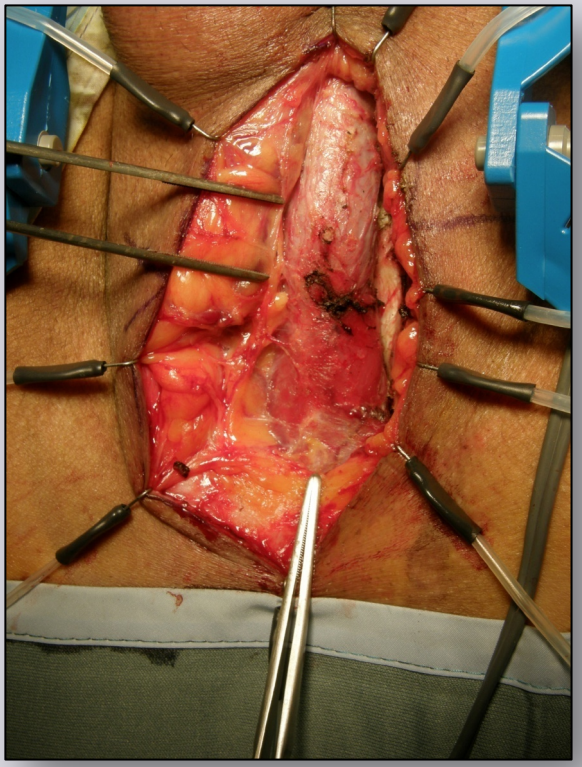
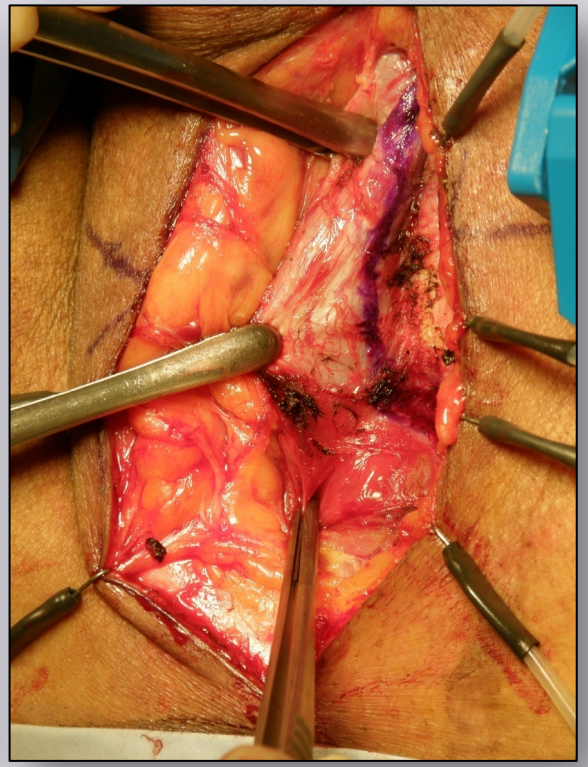
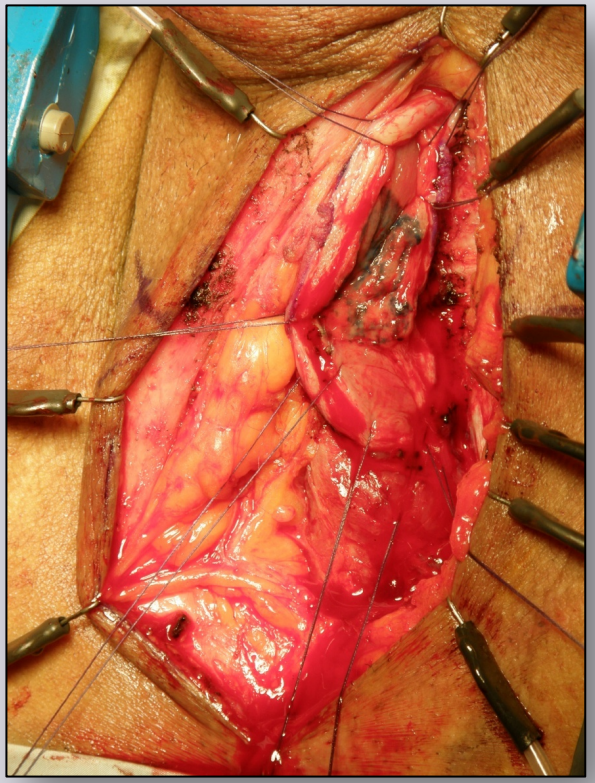
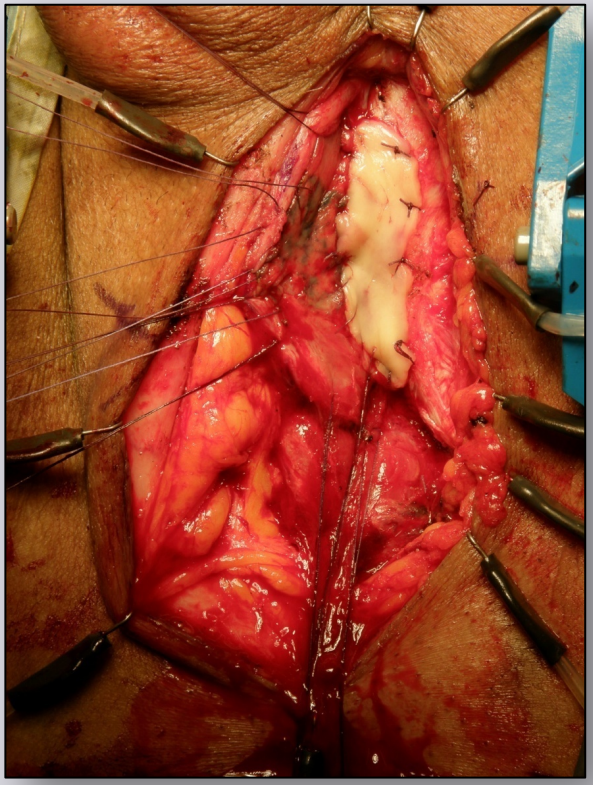
# Kulkarni's one-side graft urethroplasty

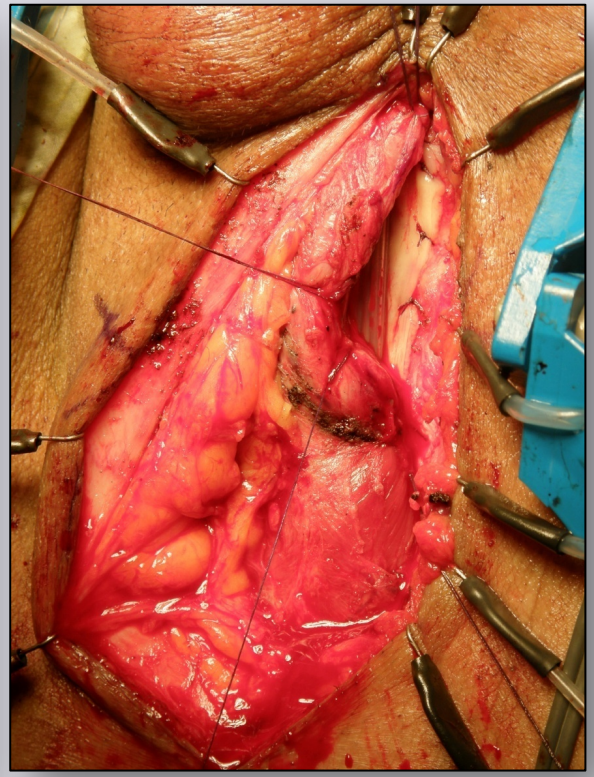


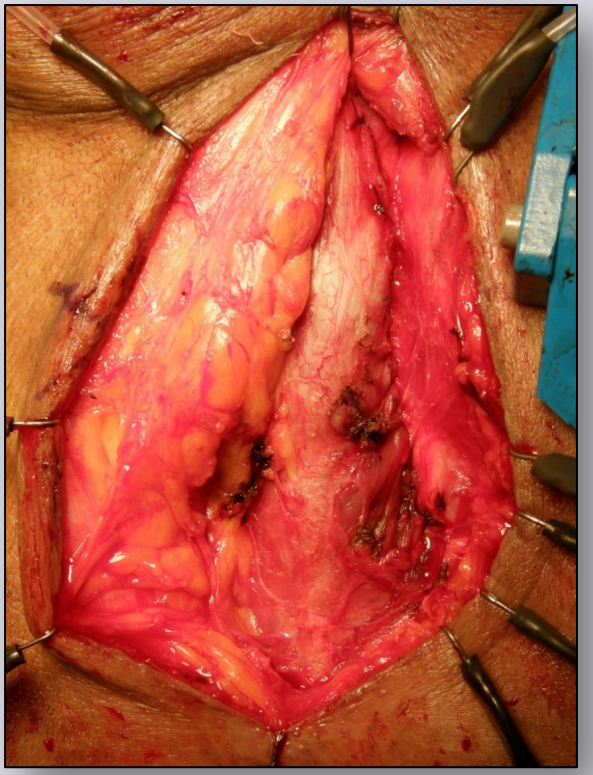




# Kulkarni's one-side graft urethroplasty







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# Non-transecting anastomotic bulbar urethroplasty: a preliminary report

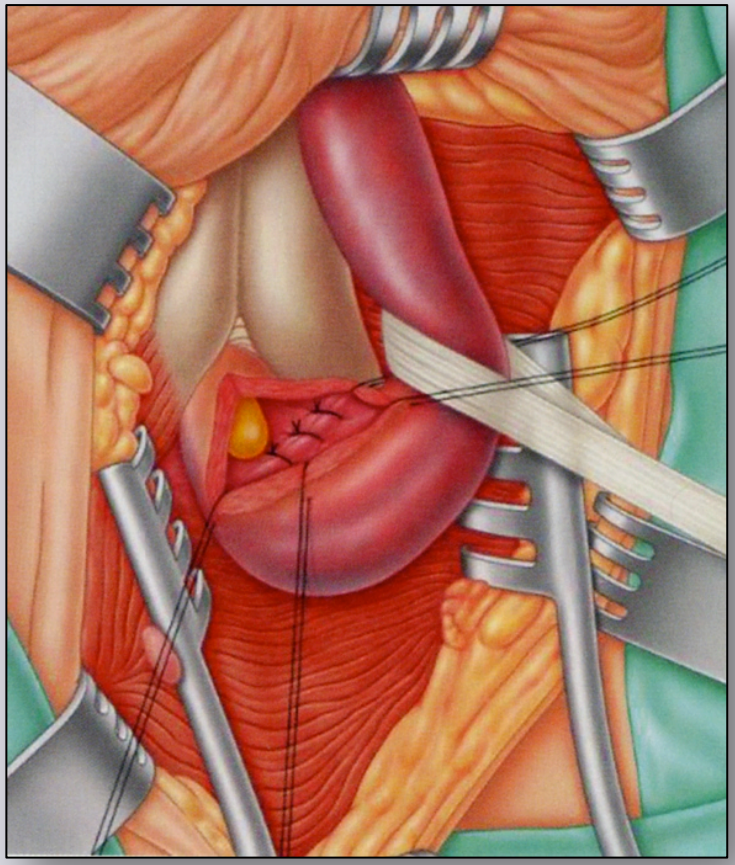
**Daniela E. Andrich and Anthony R. Mundy**

*Institute of Urology, London, UK*

Accepted for publication 21 April 2011

**BJU Int 2011, 109: 1090-1094**

**A. R. Mundy**

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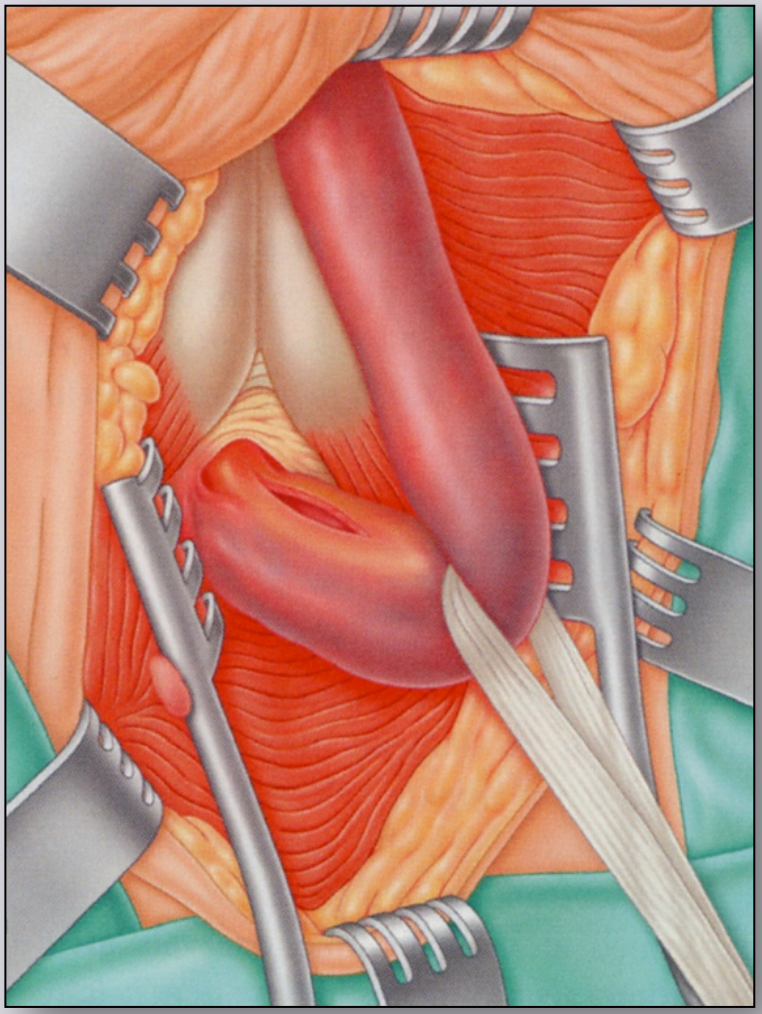
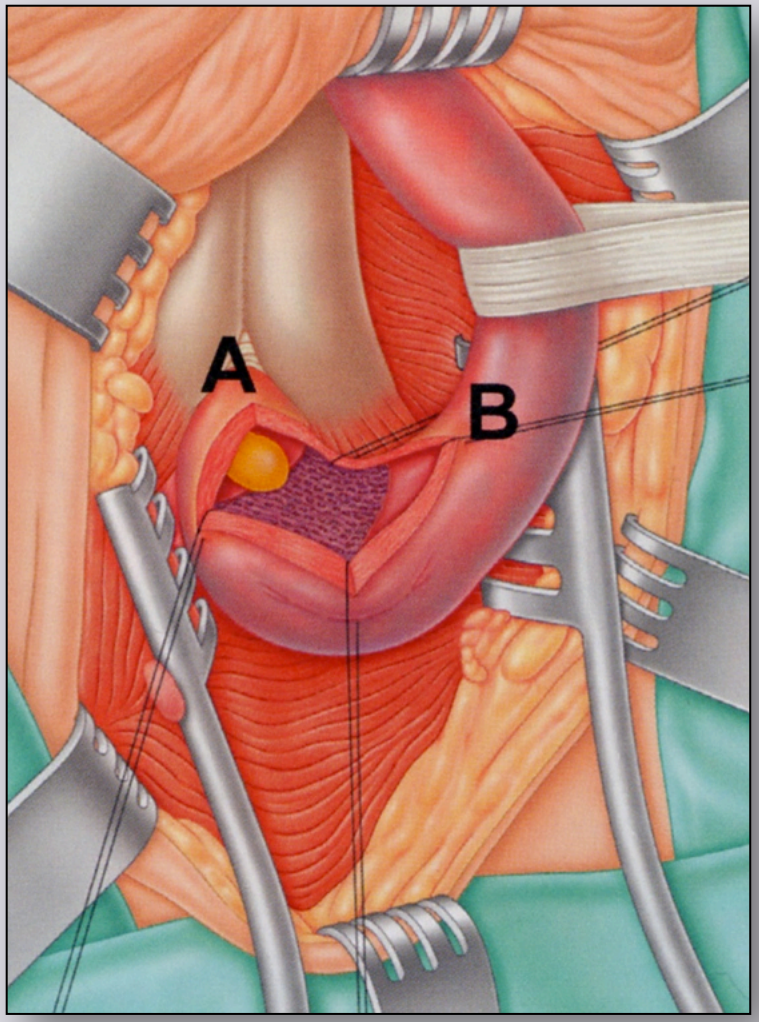
# Mundy's non-transecting bulbar urethroplasty



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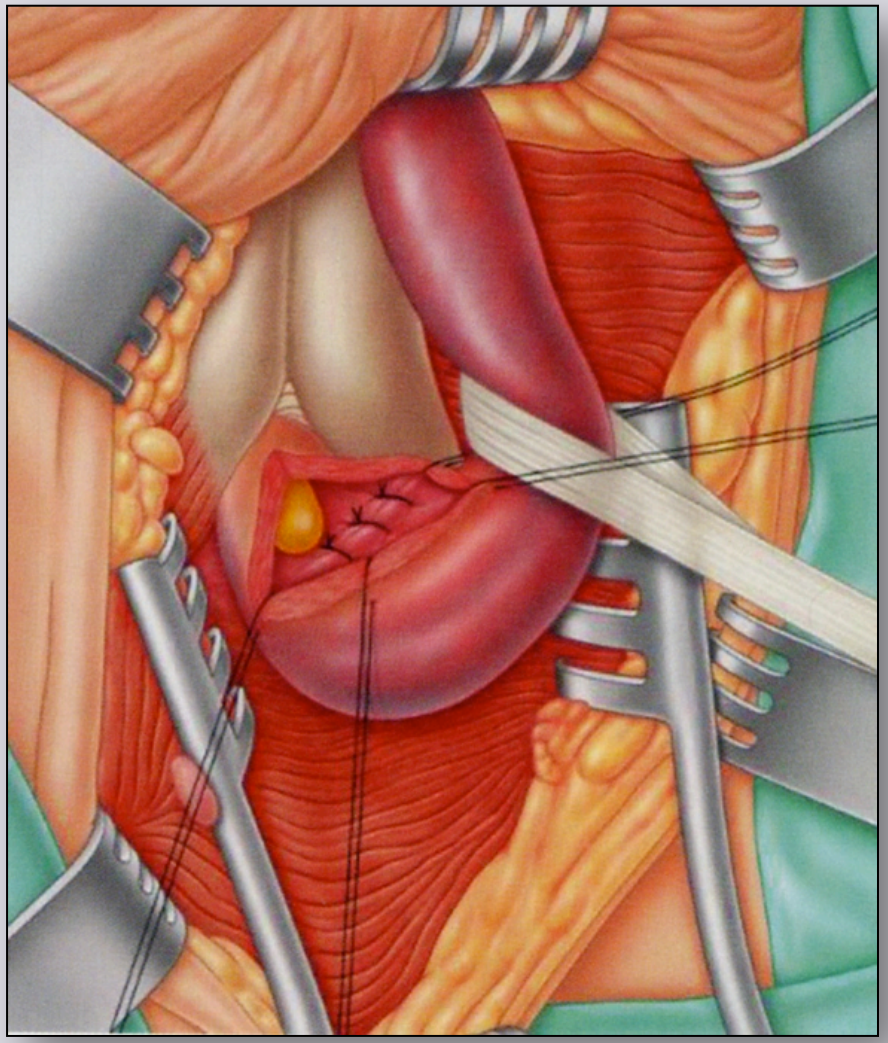
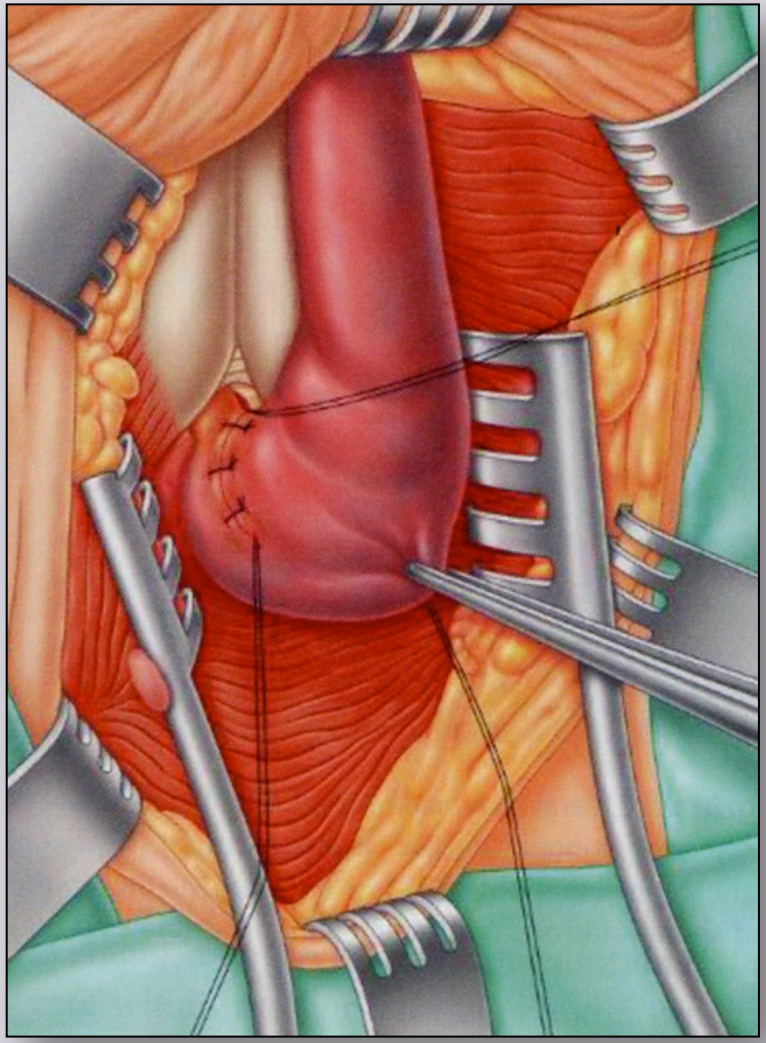
# Mundy's non-transecting bulbar urethroplasty





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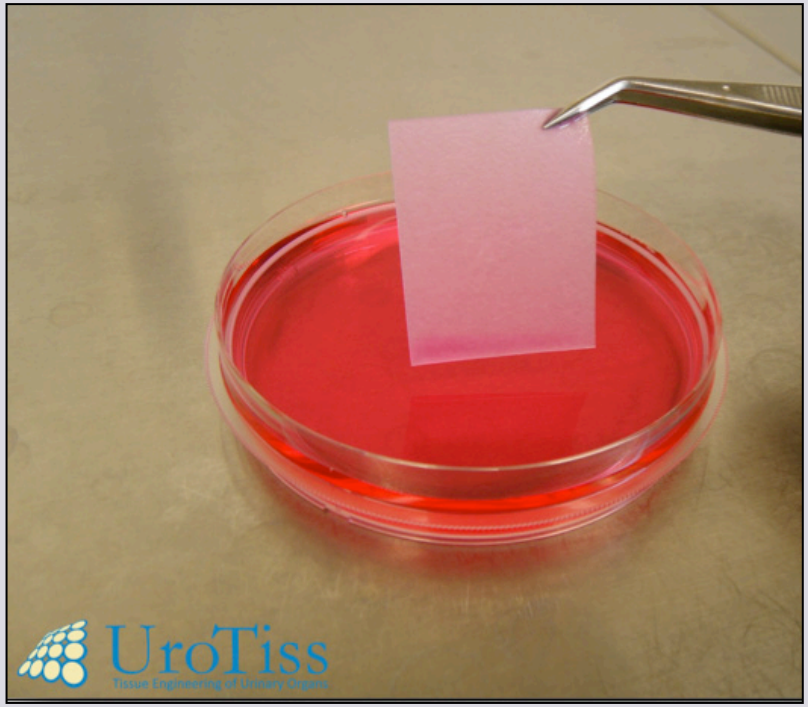
# My Journey Around the Urethra

## The Future:
## Reconstruction of the urethra using tissue engineered material



# The Lancet

## The end of the beginning for tissue engineering

For three decades we have heard about the hope of tissue engineering. Hyperbole has become routine, but amidst unreasonable expectations are serious scientists, like Paulo Macchiarini, who believe that by combining cells and degradable materials ex vivo they can develop organs to replace or repair diseased tissues. After many years of trying to build engineered tissues on a backbone of synthetic degradable polymers,[1] a growing body of evidence that the tracheal graft is now naturalised. More importantly, given the data for extracellular-matrix-derived restorative degradable materials and their use in airway and bladder neo-organ development[4,5] we can celebrate the end of the beginning for tissue engineering; the groundwork has been laid for clinical implementation in other specialties.

Excitement about tracheal regenerative therapy

**October 2013**

## Tissue engineering's green shoots of disruptive innovation

The ready availability of tissues or organs to replace or repair those diseased or damaged is a ubiquitous clinical need, and the rapidly developing field of tissue engineering might offer innovative solutions. Two Articles[1,2] in *The Lancet* show the incremental expansion of the applications of tissue-engineering technology to reconstructive surgery.

Application of cells to a scaffold, with or without added chemical or mechanical stimuli, followed by their use for repairing congenital or acquired defects was restoration of contour and nasal airflow to the noses of two women and three men, aged 76–88 years, undergoing substantial resections of external nasal tissue as treatment for skin cancer. After flap refinement at 6 months, Fulco and colleagues[2] took biopsy samples of repair tissues and histologically analysed them. Safety and feasibility of the procedure 12 months after reconstruction were the primary outcomes. Importantly, the staged reconstruction in the patients permitted histological assessment of the implanted tissue and

**April 2014**

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Asian Journal of Andrology (2013) 15, 89–92

www.nature.com/aja

REVIEW

# Tissue engineering in urethral reconstruction—an update

Altaf Mangera[1] and Christopher R Chapple[2]

**The field of tissue engineering is rapidly progressing. Much work has gone into developing a tissue engineered urethral graft. Current grafts, when long, can create initial donor site morbidity. In this article, we evaluate the progress made in finding a tissue engineered substitute for the human urethra. Researchers have investigated cell-free and cell-seeded grafts. We discuss different approaches to developing these grafts and review their reported successes in human studies. With further work, tissue engineered grafts may facilitate the management of lengthy urethral strictures requiring oral mucosa substitution urethroplasty.**
*Asian Journal of Andrology* (2013) **15,** 89–92; doi:10.1038/aja.2012.91; published online 8 October 2012

**Keywords:** reconstructive urology; tissue engineering; urethra; urethroplasty

**Asian Journal of Andrology 2013, 15 89-92**

## Laboratory

**Many researchs suggesting the use of different tissue-engineered materials**

## Operating room

**Rare clinical use of these materials in patients**

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## Tissue-Engineered Buccal Mucosa Urethroplasty—Clinical Outcomes

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[b] *Department of Engineering Materials and Division of Biomedical Sciences and Medicine, The Kroto Research Institute, North Campus, University of Sheffield, Sheffield, UK*

**Eur Urol 2008, 53: 1263-1271**

# 10 patients

## Tissue-engineered autologous urethras for patients who need reconstruction: an observational study

*Atlantida Raya-Rivera, Diego R Esquiliano, James J Yoo, Esther Lopez-Bayghen, Shay Soker, Anthony Atala*

**The Lancet 2011, 377: 1175-1182**

# Reconstruction of urethral strictures using MukoCell®, a tissue-engineered oral mucosal graft

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# Multicenter clinical experience with MukoCell implant in Germany

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Chemnitz
Hamburg
Lipsia
Luneburg
Osnabruck

70 patients

Period: from 2010 to 2013


**Dresden - Germany**

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**Worldwide, MukoCell® is the first nationally licensed tissue-engineered urologic product, legally marketed in Germany according to §4b Abs. 3 of AMG (German drug Law) with the authorization number PEI.A.11491.01.**

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AUA 2014

# Preclinical and clinical examination of tissue-engineered graft for urethral reconstruction (MukoCell®) with regard to its safety

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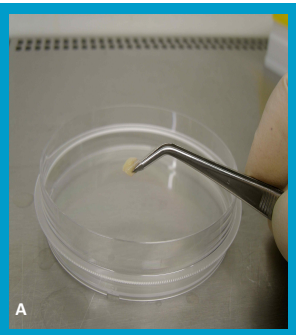
(1) 1 Centre for Reconstructive Urethral Surgery, Arezzo, Italy (2) Zeisigwald Clinics Bethanien, Department of Urology, Chemnitz, Germany (3) San Donato Hospital, Department of Urology, Arezzo, Italy (4) St. Hedwig Krankenhaus, Department of Urology, Berlin, Germany (5) UroTiss GmbH, Dresden, Germany

## I. Introduction

MukoCell® is a national authorized, autologous tissue-engineered oral mucosa graft. The present report sums up some of MukoCell®' s preclinical safety data. Additional reported data of 70 patients, treated with MukoCell®, are also considered with regards to safety analysis.



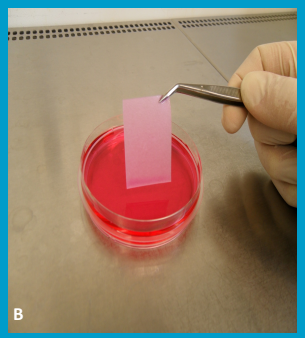




Fig. 1: Patient's oral mucosa cells are generated from a small oral mucosa biopsy (A) and cultured on the surface of a biocompatible scaffold (B).

Source of Funding: UroTiss GmbH, Germany

## II. Methods

For MukoCell® production, patient's oral mucosa cells were generated from a small oral mucosa biopsy and cultured on the surface of a biocompatible scaffold (Fig. 1).

The tumorigenic potential of MukoCell® was examined in vivo. For this purpose, human cultured cells of 4 different runs were injected by intraperitoneal and subcutaneous route into each of ten immunodeficient athymic nude mice. $4x10^7$ cells ± $2 \times 10^6$ cells were injected into each animal on Days 1, 18, 25 and 46 of the study. An additional group consisting of ten animals each received cell culture medium as vehicle control (Table 1).

To examine the potential migration of cells into distant organs, murine MukoCell® constructs from eGFP-transgenic mice were implanted into peritoneal cavity of histocompatible non-transgenic mice and vice versa. The 24 test animals were sacrificed either at weeks 1, 2, 4 or 12 for histological analysis (Table 2).

To investigate the degradation of implanted MukoCell® with time, scaffolds with the size of 0.5 x 1.5 cm were implanted into the peritoneal cavity of 20 BALBc/C57BL6J mices.

Additionally, reported clinical safety data from 70 MukoCell®-treated patients with urethral stricture, which have been recruited in an ongoing observational study with up to 2 year follow-up period, were evaluated on the basis of a pharmacivigilance system. Ethical committee votum was available for the study.

## III. Tables

Table 1. Experimental groups allocated during the tumourigenicity study

| Group | No. of animals | Item | Injection on days[a)] | Injection volume (i.p. + s.c.) [µL] | Total no. of cells at each day |
|---|---|---|---|---|---|
| 1a | 5 | Test items (n=4) | 1, 18, 25, 46 | 200 + 200 | $10^7 \pm 2 \times 10^6$ |
| 1b | 5 | Test items (n=4) | 1, 18, 25, 46 | 200 +200 | $10^7 \pm 2 \times 10^6$ |
| 2a | 5 | Control item | 1, 18, 25, 46 | 200 + 200 | - |
| 2b | 5 | Control item | 1, 18, 25, 46 | 200 + 200 | - |

Notice [a)] Cell preparations generated independently from four different runs were used. A separate cell preparation was used on each injection day.

Table 2. Allocation and treatment of animals in the biodistribution study

| Group (Cage) | No. of animals | Donor for engineered tissue graft | Recipient of engineered tissue graft | Sacrifice after implantation week |
|---|---|---|---|---|
| A-1 (11/5/0) | 3 | EGFP-tg | nontg | after 1 week |
| A-2 (11/6/0) | 3 | EGFP-tg | nontg | after 2 weeks |
| A-3 (11/7/0) | 3 | EGFP-tg | nontg | after 4 weeks |
| A-4 (11/8/0) | 3 | EGFP-tg | nontg | after 3 months |
| reserve animal (11/H3/0) | 1 | EGFP-tg | nontg | |
| B-1 (11/1/0) | 3 | nontg | EGFP-tg | after 1 week |
| B-2 (11/2/0) | 3 | nontg | EGFP-tg | after 2 weeks |
| B-3 (11/3/0) | 3 | nontg | EGFP-tg | after 4 weeks |
| B-4 (11/4/0) | 3 | nontg | EGFP-tg | after 3 months |
| reserve animal (11/H1/9) | 1 | nontg | EGFP-tg | |

Notice: Material used for histology after sacrifice: Brain (cerebrum, cerebellum, brain stem, paraventricular parts); heart; kidneys;

large intestine (caecum, colon, rectum); liver; lung; lymph nodes (mesenteric)

intestine; (duodenum, jejunum, ileum) / peyer plaques; spleen; thymus; transplants (including surrounding tissue)

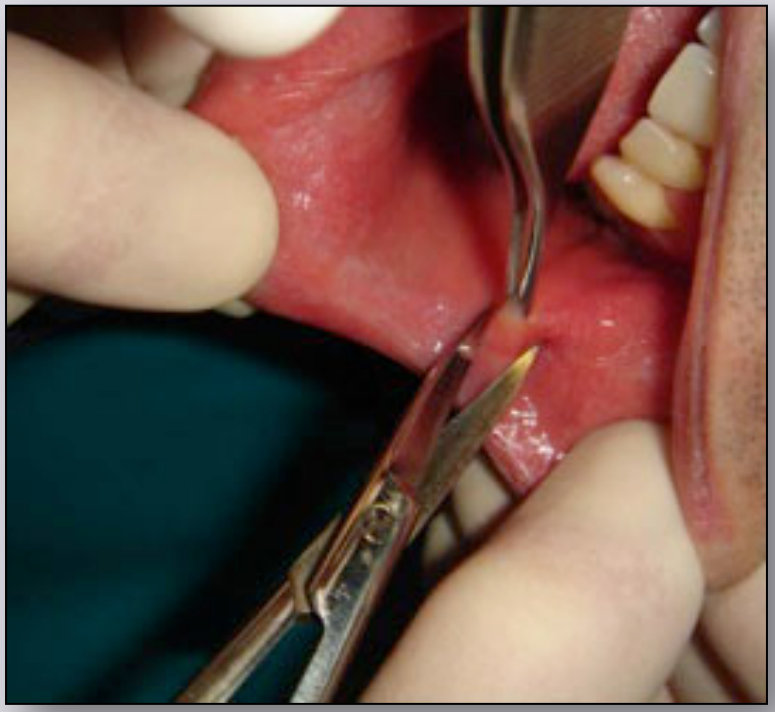
## IV. Results

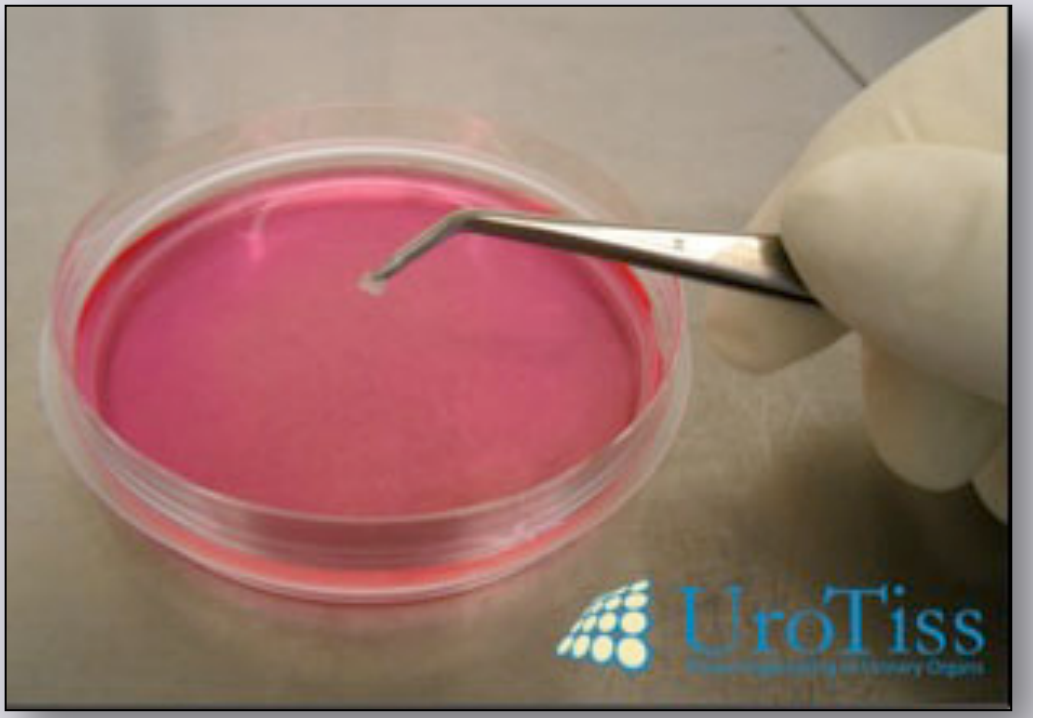
Evaluation of tumorigenicity study in nude mice did not reveal macroscopic and microscopic malignancies attributable to MukoCell® in 60 different examined tissues and organs. Additionally, migration of the transplanted cells into distant organs was excluded at all examined time intervals after implantation of murine homologue of MukoCell®. While the grafts were still present in all 10 animals 9 days after implantation, 6 of 10 grafts were degraded 40 days after implantation in the remaining 10 animals. Clinical data of 70 with MukoCell® treated patients demonstrated no peri- or post-operative adverse events related to MukoCell®.

## V. Conclusion

MukoCell® seems to be a safe graft for urethroplasty for patients with urethral stricture. The graft is degrading within a few weeks and hence avoids complication associated with persistent implants.

# Local anaesthesia





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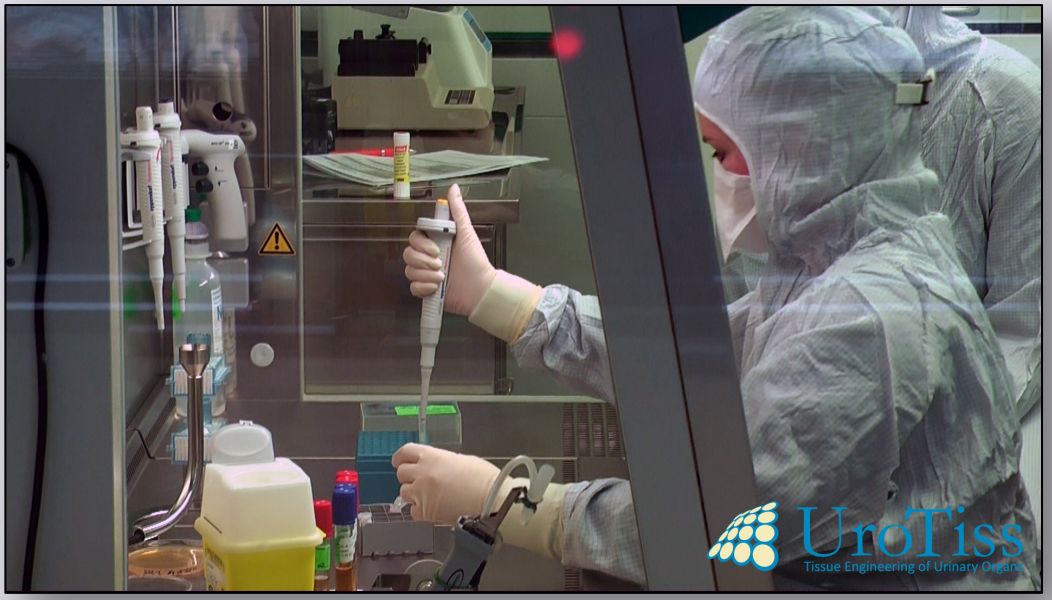
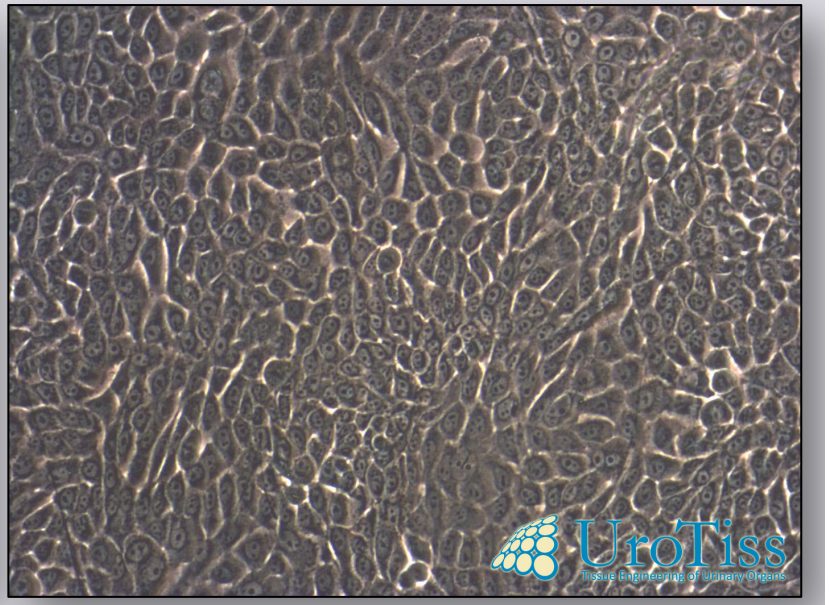
Tissue Engineering of Urinary Organs




**In the GMP laboratory, the oral cells were expanded and cultured on the surface of a biocompatible scaffold**

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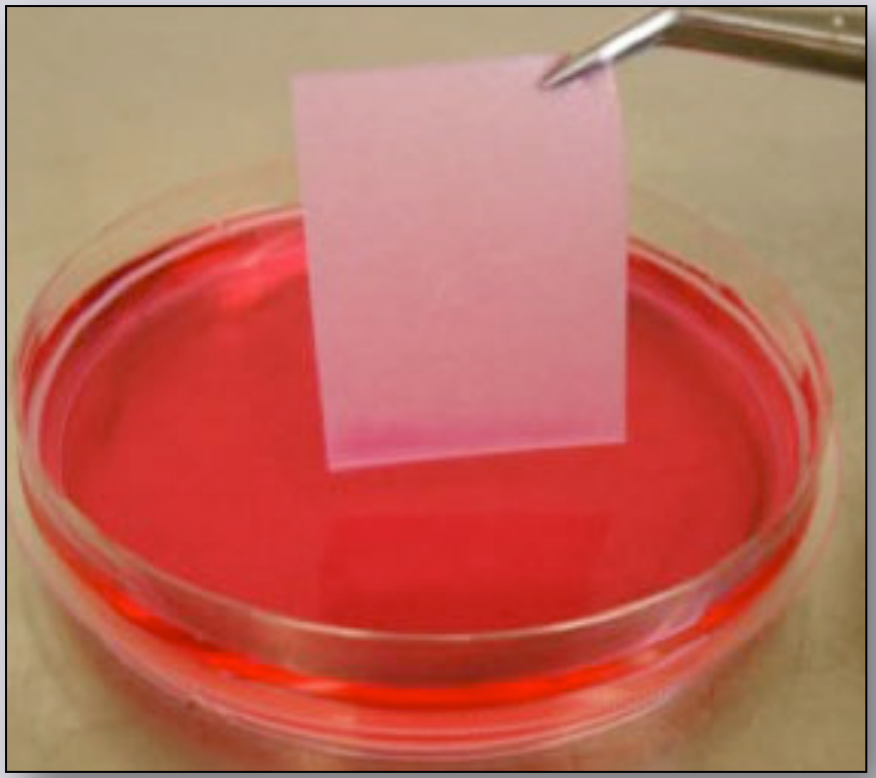
# MukoCell



3 weeks later

48 hours for transplant

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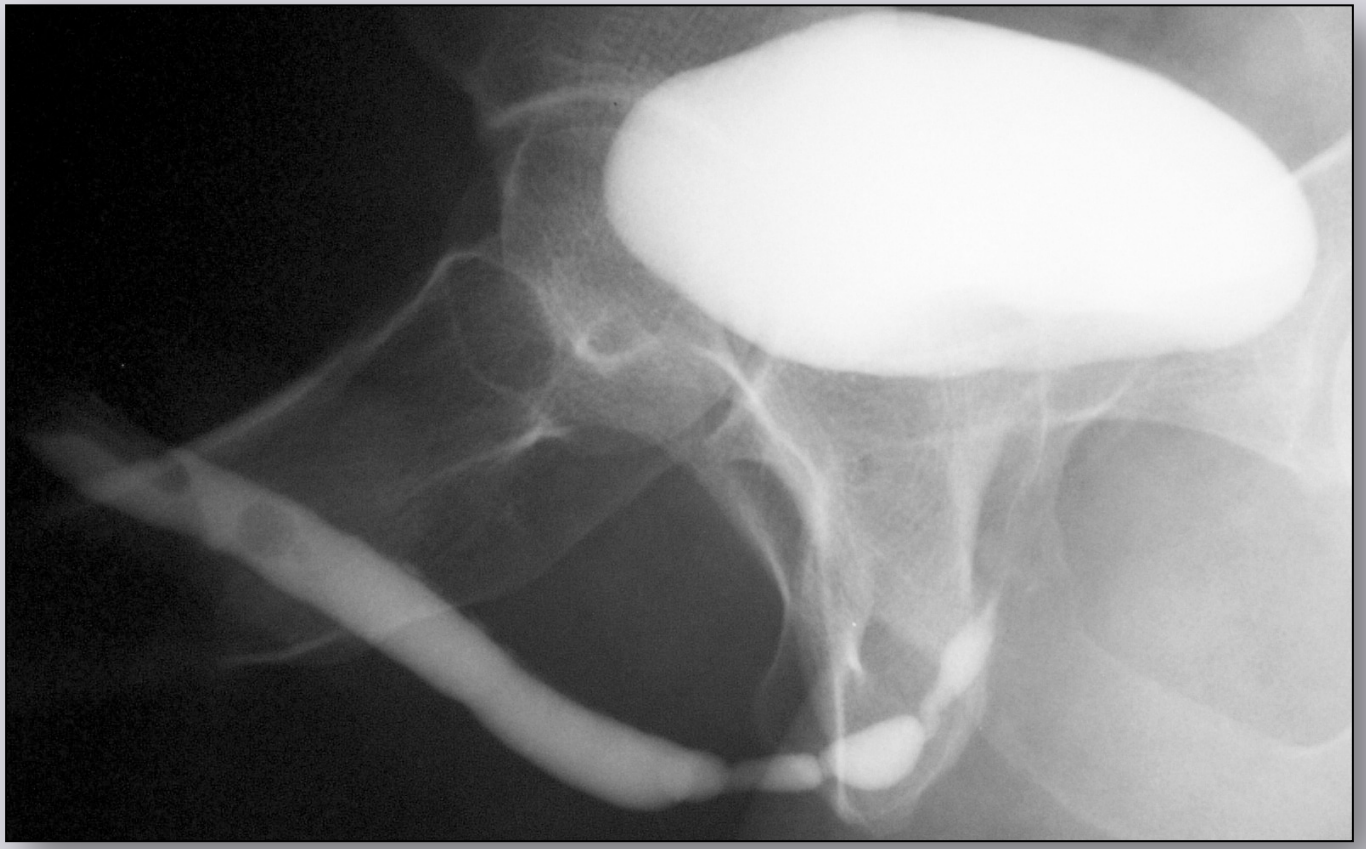

**On this preliminary phase of the study we decided to include only patients with bulbar urethral stricture ranging from 2 to 6 cm in lenth. The aim of our preliminary study was investigating the safety, feasibiity and effectiveness of MukoCell in urethral reconstruction.**

# Surgical transplant of the MukoCell®

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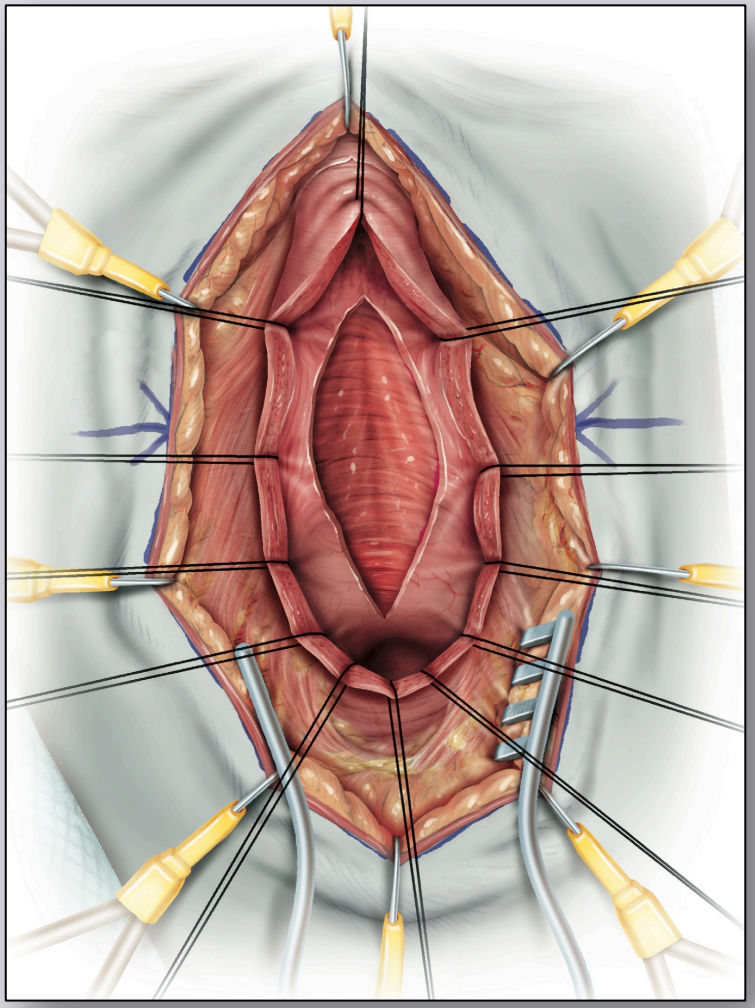
# Dorsal inlay technique



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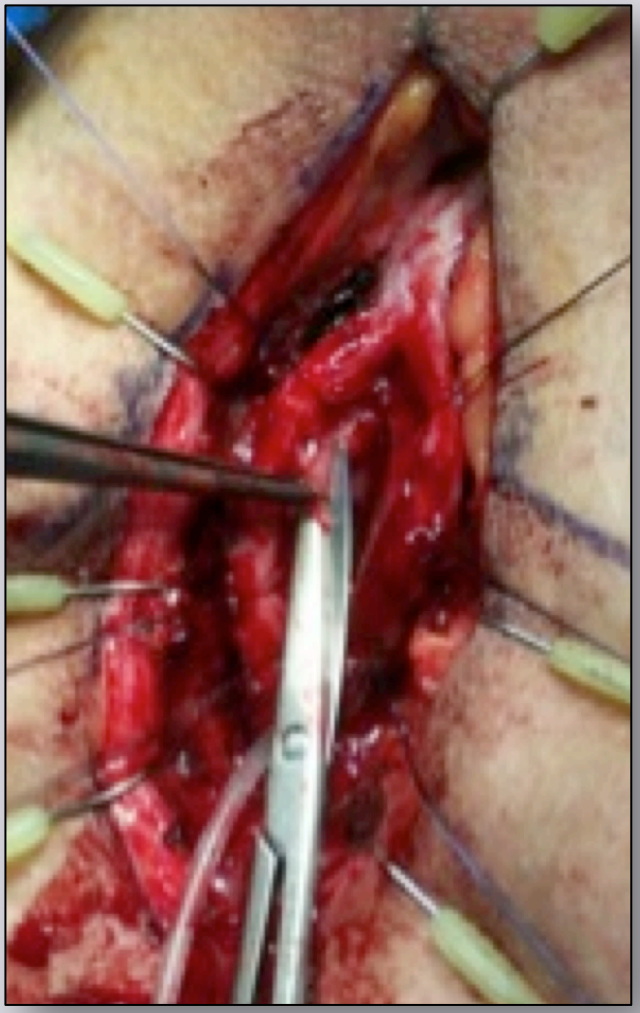
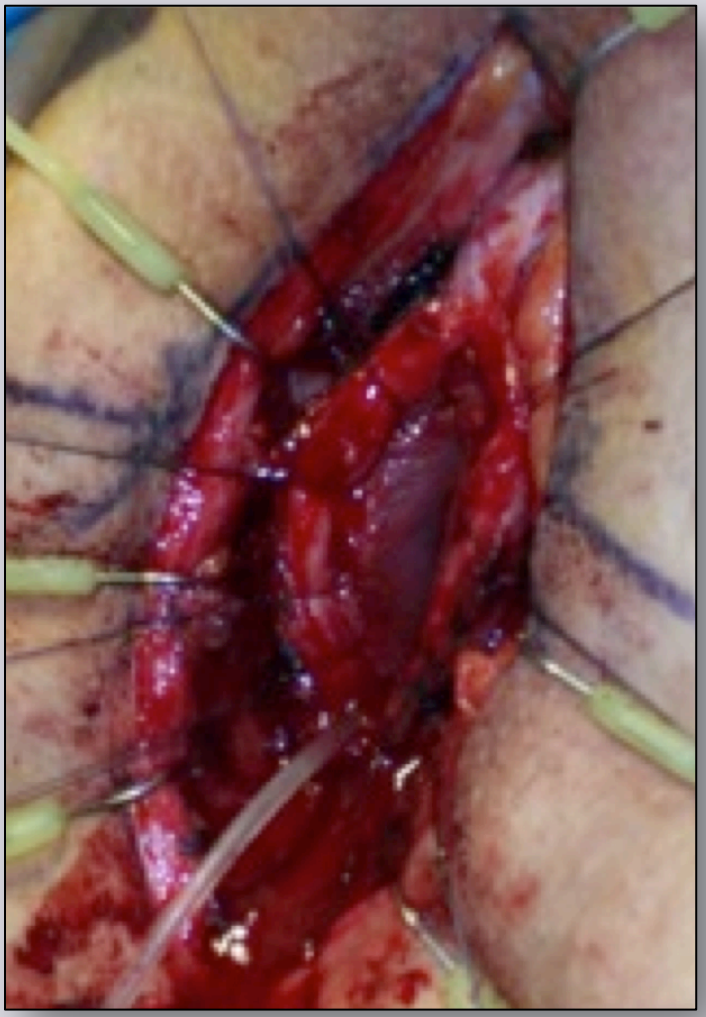
# Dorsal inlay technique





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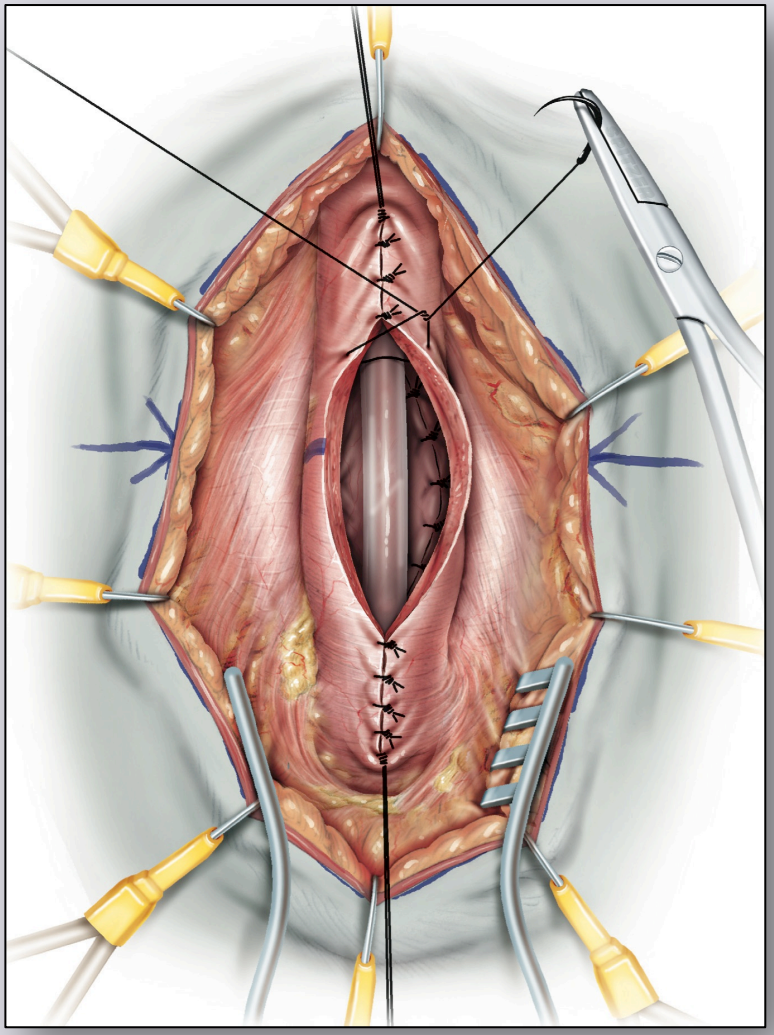
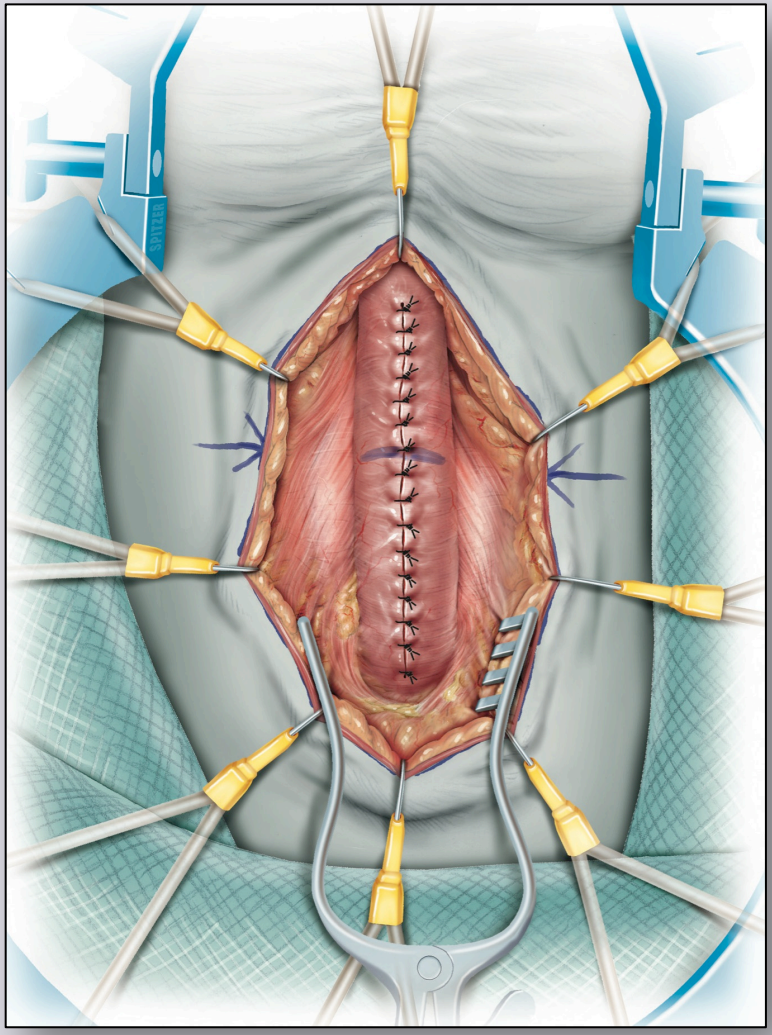
# Dorsal inlay technique





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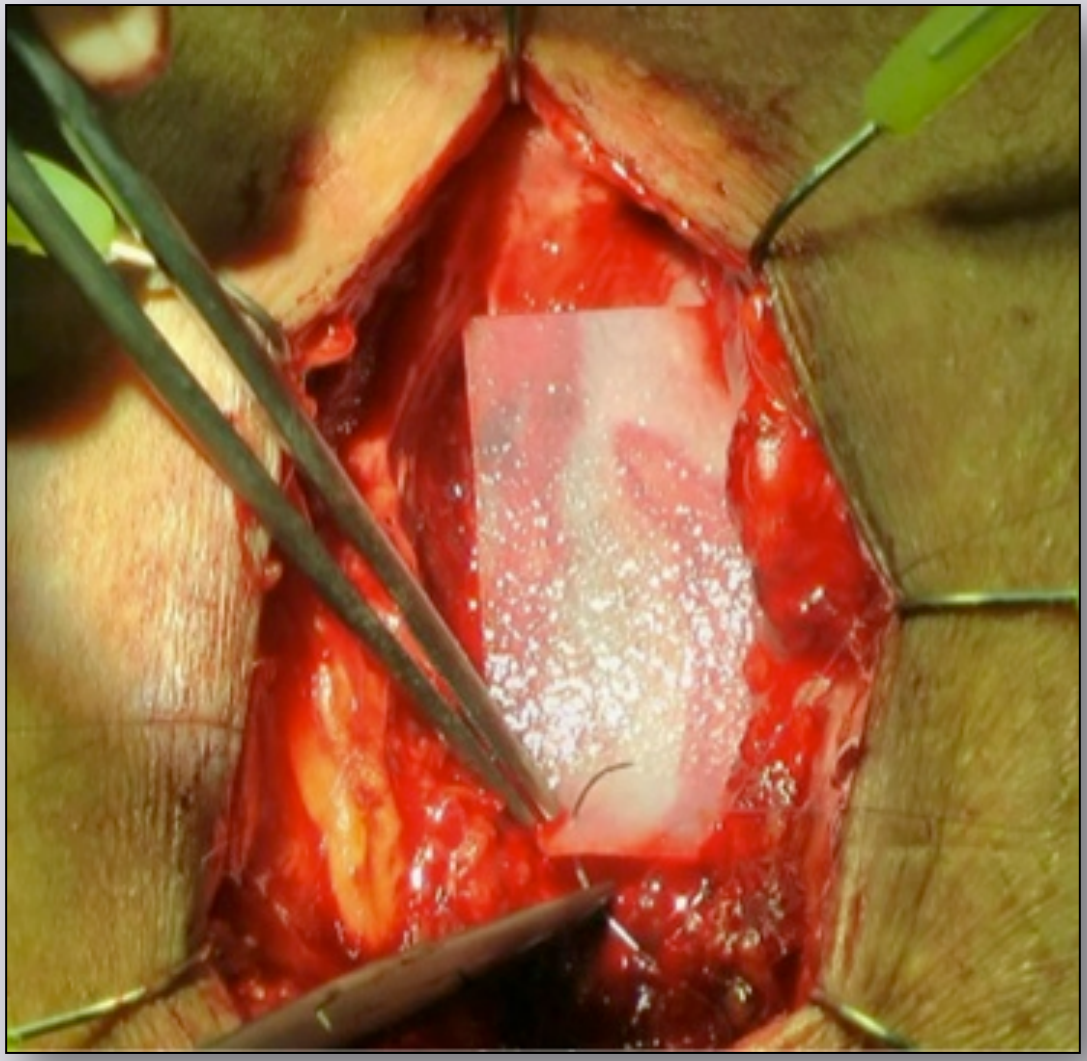
# Ventral onlay technique



# Post-operative voiding cysto-urethrography

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# Multicenter clinical experience with MukoCell implant in Germany

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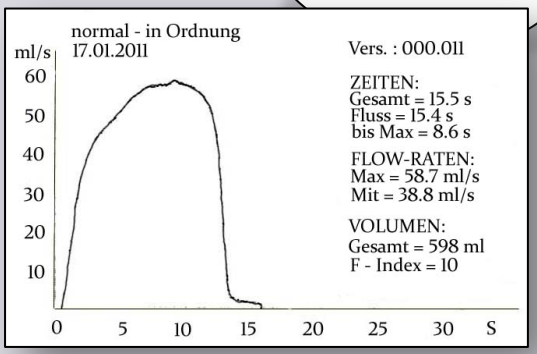
**Chemnitz**
**Hamburg**
**Lipsia**
**Luneburg**
**Osnabruck**

**70 patients**

**Period: from 2010 to 2013**




**Overall success rate: from 82% to 85%**

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# Limitations of this study

- Selected series of patients
- Short follow-up

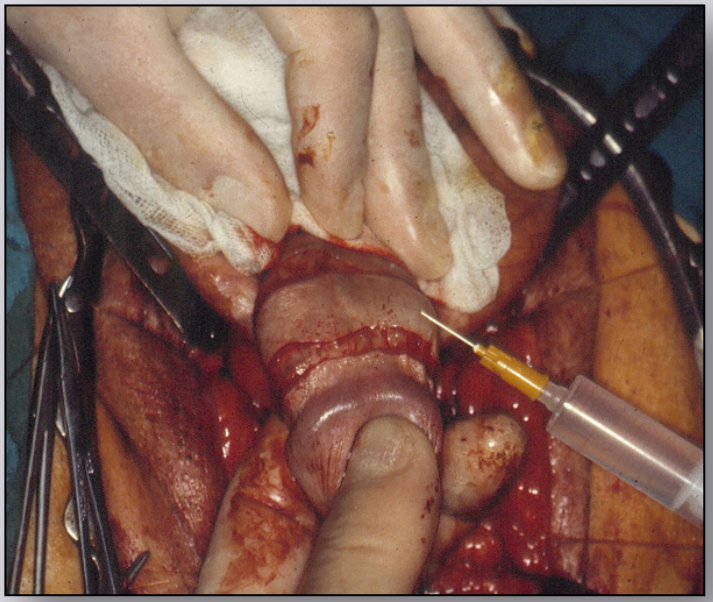
✓ This material should be used only in Germany

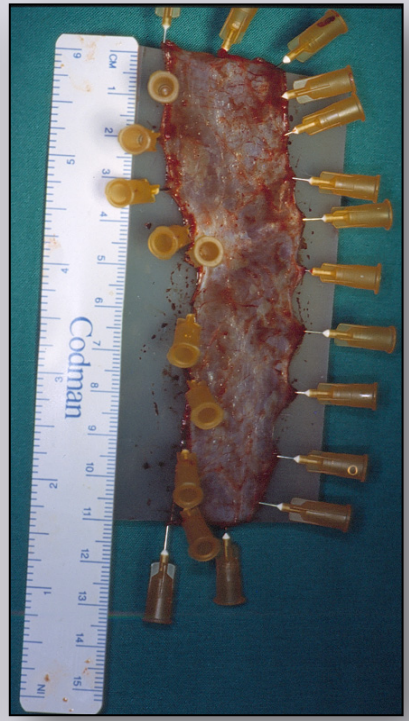
✓ The cost is about 4.000,00 to 5.000,00 Euro

✓ This material should be used in 48 hours

# My Journey Around the Urethra

## Conclusions

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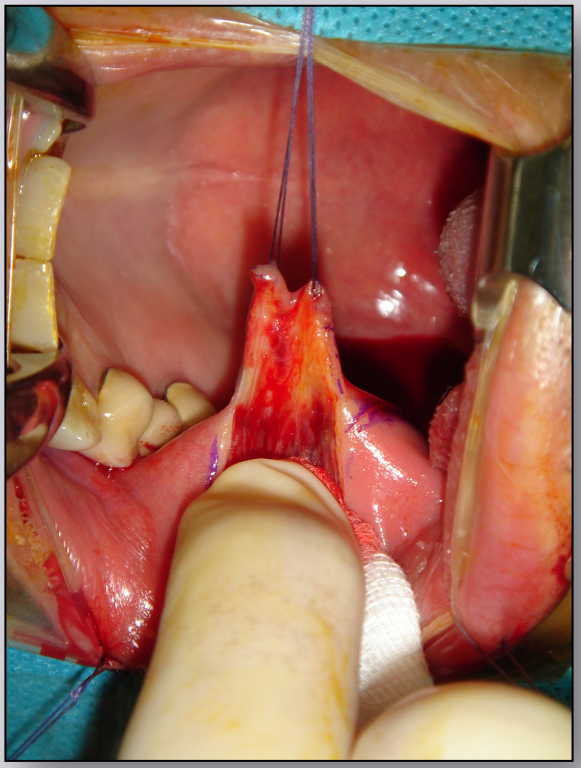
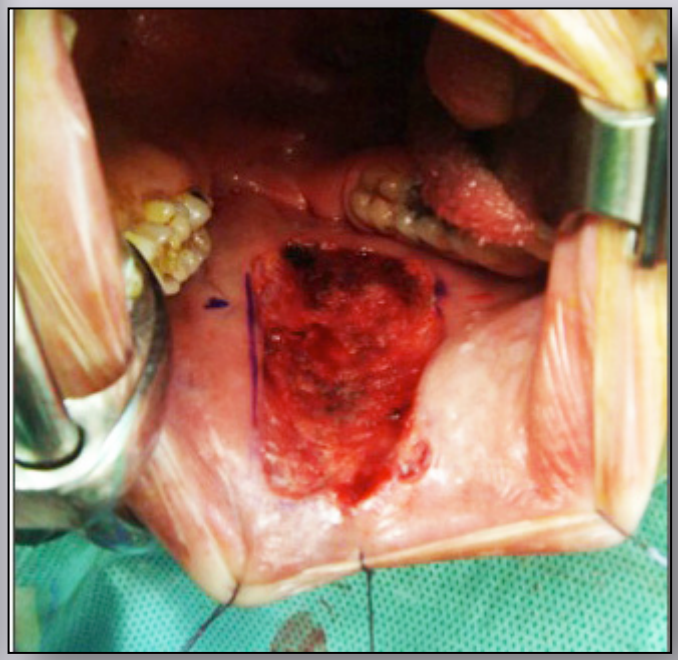
# My Journey Around the Urethra

## Conclusions





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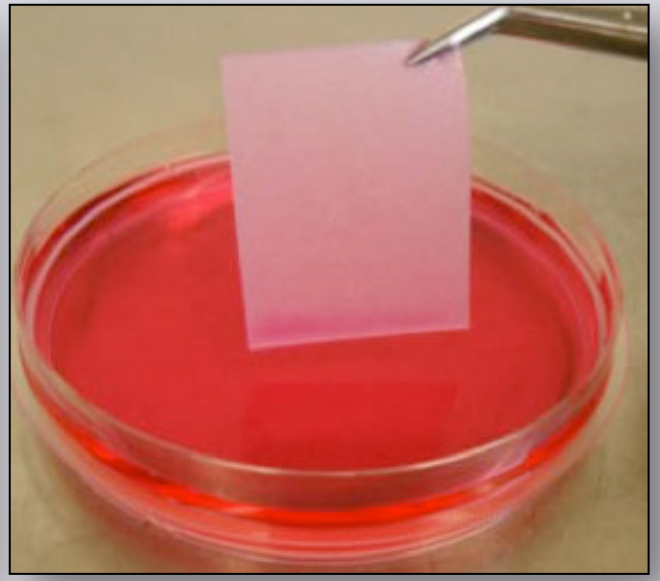
# My Journey Around the Urethra

## Conclusions



## Future

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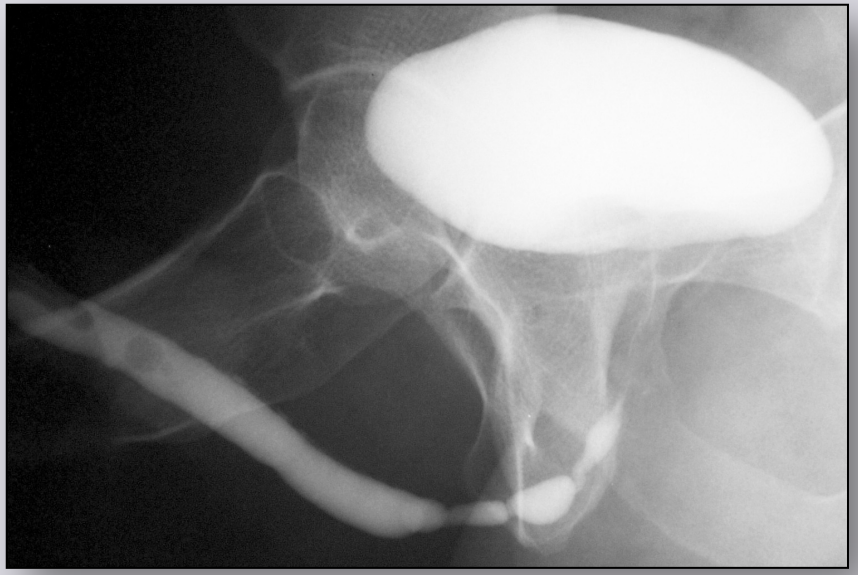
# MukoCell for urethral reconstruction



Today

Tomorrow

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1987


2014

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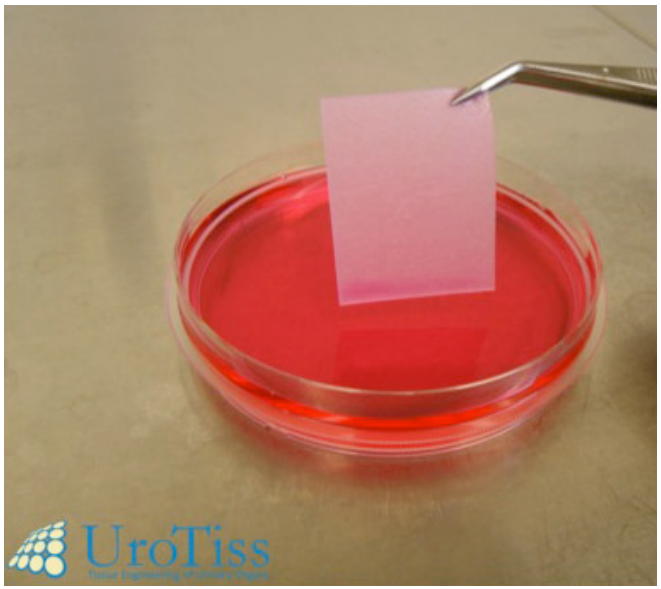


2014

**MukoCell is now only a first step for a new future of urethral reconstruction.**

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**“ As I look back on my career I realize that the most important rewards were always those where I touched the lives of others – be they patients, staff or trainees, and this I hope is a goal to which all physicians aspire.**

**Thank you for this opportunity to present these personal thoughts”**

**George D. Webster**