CENTER FOR RECONSTRUCTIVE URETHRAL SURGERY

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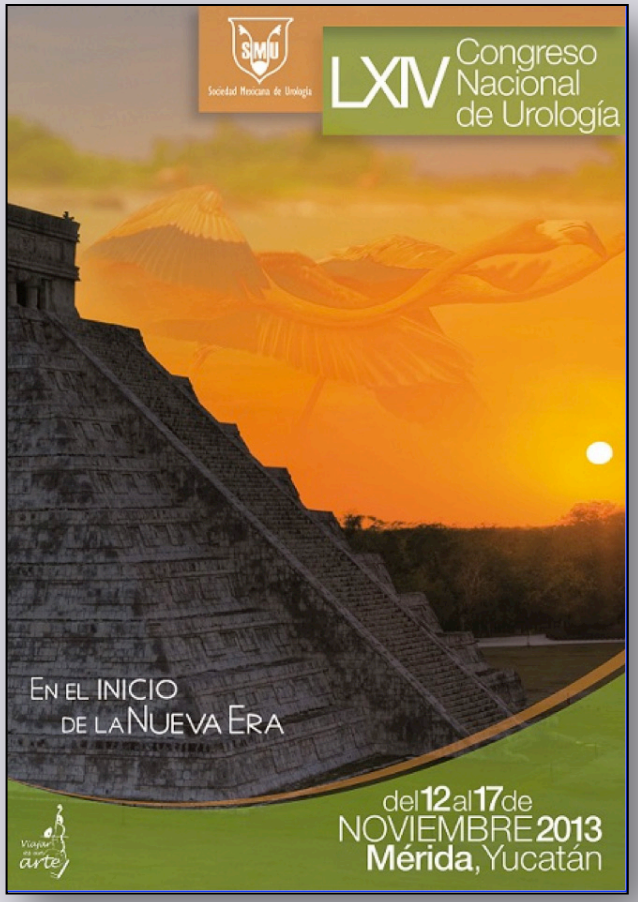

Uretroplastía usando ingeniería tisular de mucosa oral

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The end of the beginning for tissue engineering

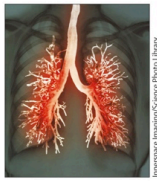
For three decades we have heard about the hope of tissue engineering. Hyperbole has become routine, but amidst unreasonable expectations are serious scientists, like Paulo Macchiarini, who believe that by combining cells and degradable materials ex vivo they can develop organs to replace or repair diseased tissues. After many years of trying to build engineered tissues on a backbone of synthetic degradable polymers,[1] a growing body of evidence suggests that decellularised whole organs and tissues are clinically effective degradable scaffolds.[2] Until recently, decellularised tissues were used clinically without the addition of cells, and in many cases—eg, the decellularised porcine small intestine submucosa family of surgical implants—this approach was sufficient to generate a healing response. The idea of whole organ engineering—whereby organs are decellularised and then repopulated with desired mixtures of cells—seems to be a realistic path towards complex three-dimensional tissue engineering.

In 2008, Macchiarini's team announced that they had successfully grown a neo-trachea from a decellularised human trachea.[3] We were reminded of the pioneering clinical implantation of a partial neo-bladder in the 1990s,[4] and the sobering reality that an exciting first clinical experience can be separated by decades from even potential clinical implementation. In *The Lancet*, Alessandro Gonfiotti and coworkers report 5-year follow-up of the tracheal implantation,[5] and do not shy away from the harsh realities of a field that begs for even broad clinical implementation while researchers are still learning how to harness our understanding of the biology. Whole organ tissue engineering is akin to converting a Ford into a Ferrari while driving at top speed. The approach is elegant but fraught with challenges and opportunities for improvement; few medical advances have needed a complete biological understanding before implementation.

Tissue-engineered airway transplantation was achieved by seeding a decellularised graft with autologous stem-cell-derived epithelial cells and chondrocytes. Concerns that autologous stem cells might give rise to tumours have been allayed after careful follow-up.[5] Indeed, use of mesenchymal stem cells in clinical trials has shown that delivery of these cells (autologous or allogeneic) is safe.[6] Gonfiotti and colleagues present compelling 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 might be muted by realisation that the patient in this study was not restored to full health. Although heroic in complying with the needs of a research study, the patient is suffering from ongoing complications from scarring at the proximal anastomotic site. There is nothing unusual about a tracheal stricture forming at a surgical site and, in fact, this patient had already had such a post-surgical stricture. Rather, the formation of a stricture shows that the remaining challenges for tissue engineering of thin hollow organs such as trachea, oesophagus, intestine, blood vessels, and bladder relate to how neo-tissues are incorporated into existing structures. Research is needed to understand how to minimise scarring at anastomotic sites, particularly for a graft that is itself degrading, releasing biological signals, and regenerating in vivo. Degradable inductive scaffolds are not biologically inert because they are replaced by native tissue, and how these scaffolds are attached and introduced to the vasculature will affect the degree to which inflammation-driven versus regeneration-driven healing takes place. For this patient, the reward of maintaining the airway and lung had to be balanced by undergoing multiple imaging studies, biopsies, and dilations. Perhaps as much can be learned from the absence of a distal stricture as from the presence of an intractable proximal stricture. Either way, the patient has enjoyed (as shown by quality of life data) 5 years of life, with less than 2% of the time in hospital being treated for the stricture.

Despite this glimpse of a clinically relevant future, several challenges need to be addressed. How long should a cell–material construct be incubated ex vivo compared with in vivo? Much of the clinical effect of extracellular matrices—which have been implanted in millions of patients as inductive wound healing scaffolds—has been derived without preseeding the matrix. Research is needed to understand what happens



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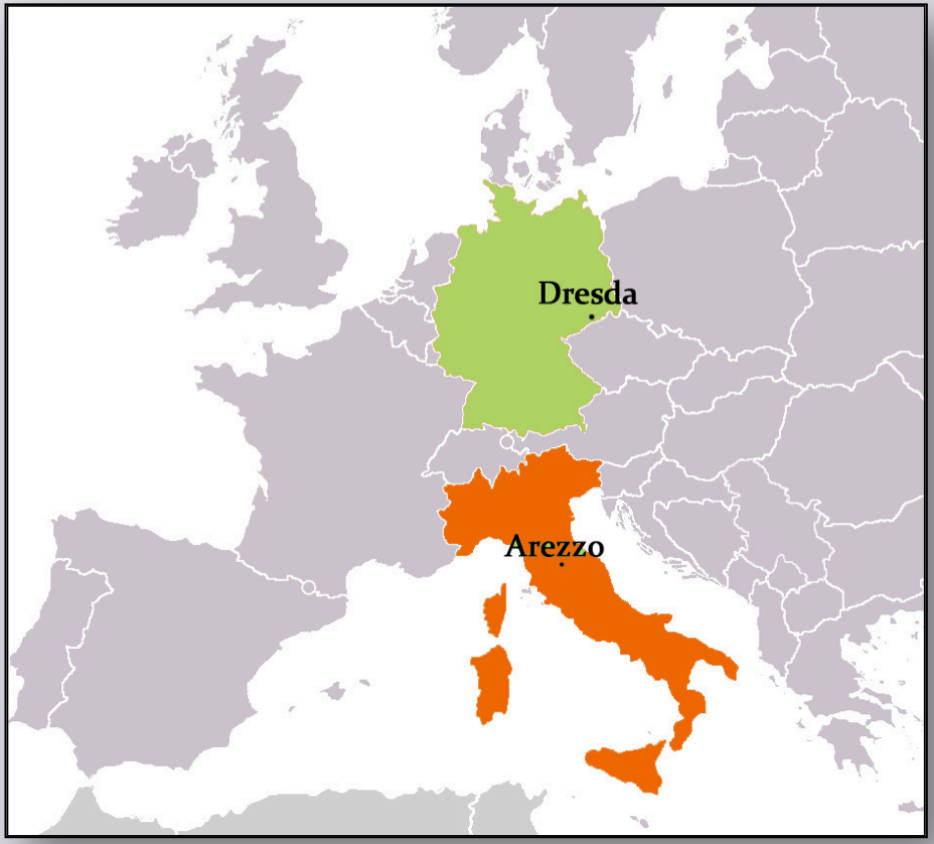
The Lancet, October 2013

Repair of the anterior urethra is one of the most demanding surgical problems in urology. In recent years, regenerative medicine and tissue engineering studies have led to the development of novel biomaterials for urethral repair.

Here we describe the first clinical report of a homogeneous series of patients who underwent tissue-engineered oral mucosal graft urethroplasty for bulbar urethral stricture.

Dr. Gouya Ram-Liebig and Dr. Soren Liebig
UroTiss GmbH – Dresden - Germany



Prof. G. Barbagli and Dr. G. Romano
Center for Reconstructive Urethral Surgery – Arezzo - Italy

Dresden - Germany

UroTiss GmbH is a pharmaceutical company, founded in Germany in 2005 by Dr. Gouya Ram-Liebig and Dr. Soren Liebig. UroTiss provides products with highest safety and quality, in accordance to current Good Manufacturing Practices (GMP).

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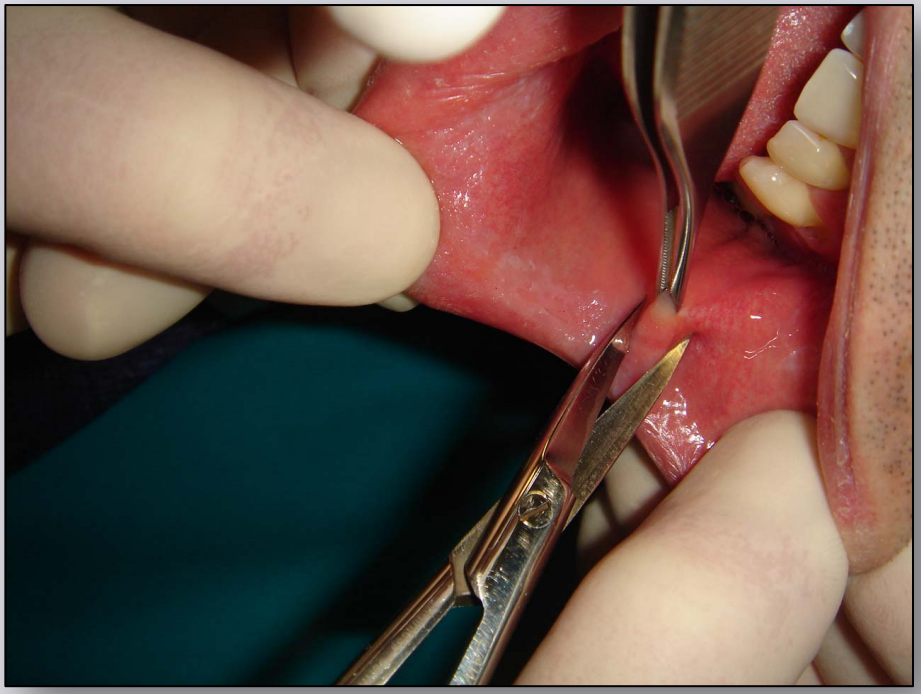
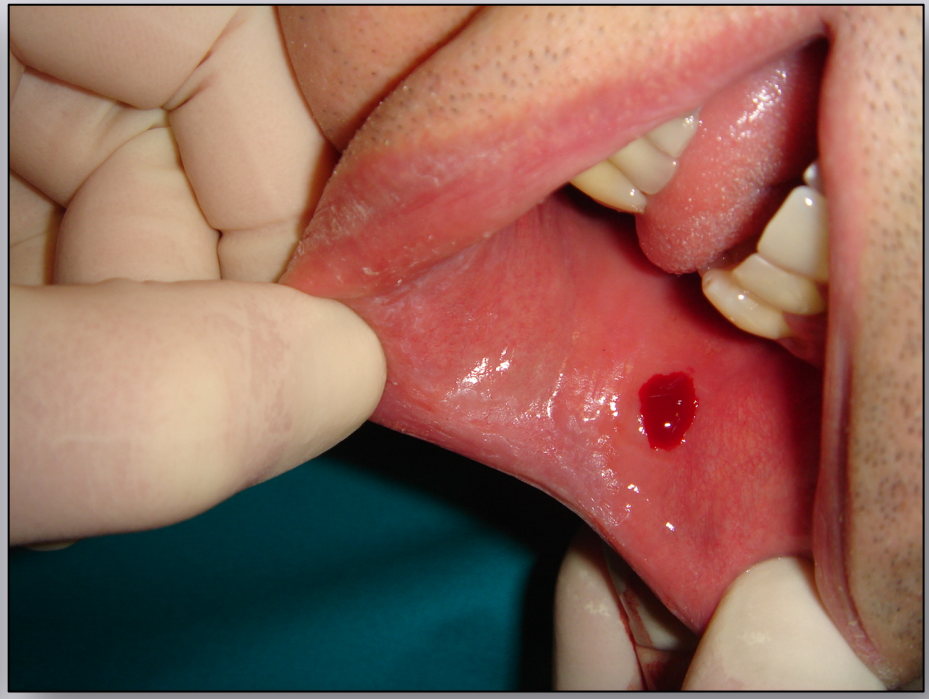
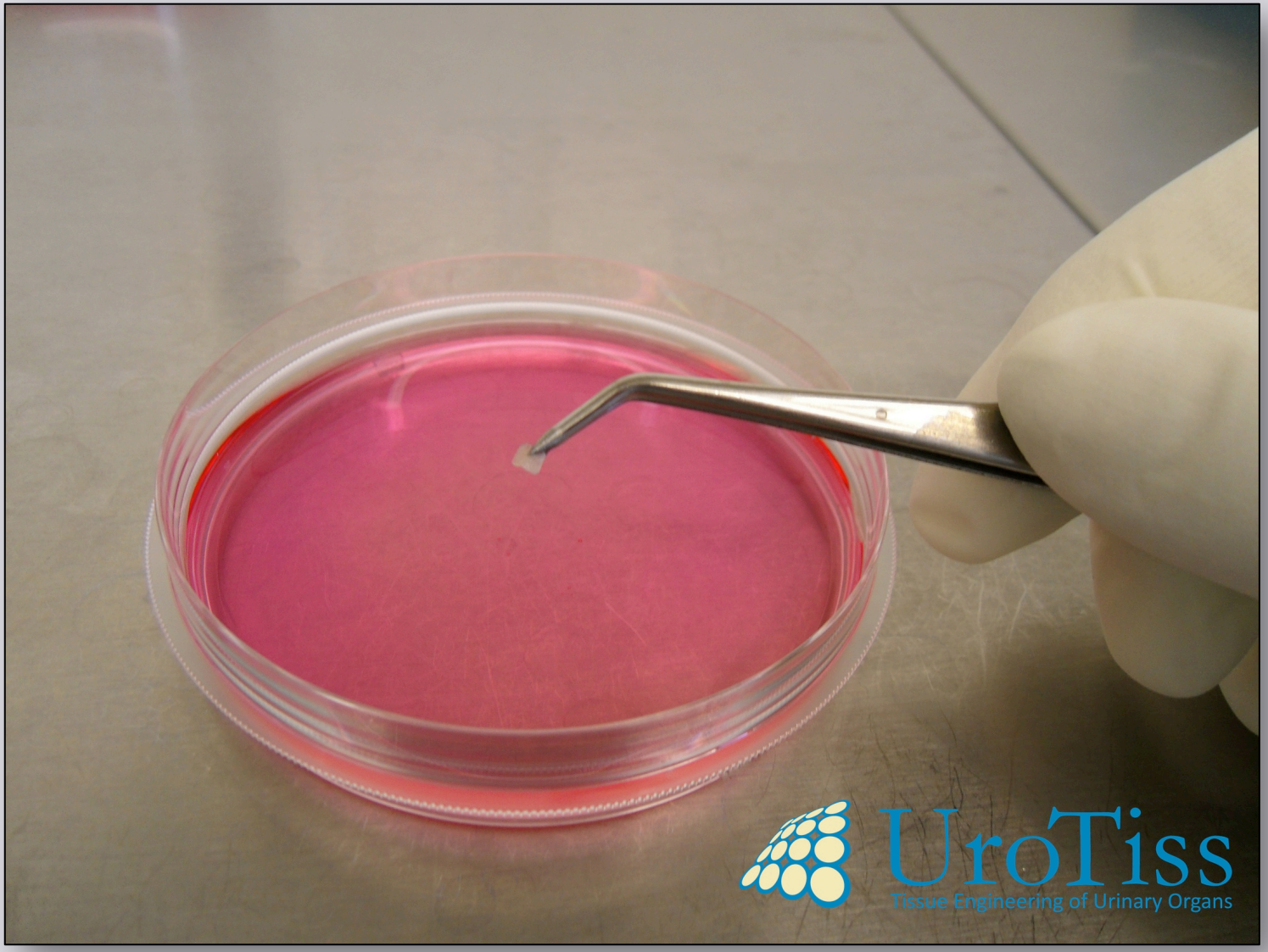
Step 1

Harvesting sample from the cheek

Local anaesthesia







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Step 2

Factory

UroTiss

Tissue Engineering of Urinary Organs

Clean roon Laboratory in accordance to current Good Manufacturing Practices (GMP).

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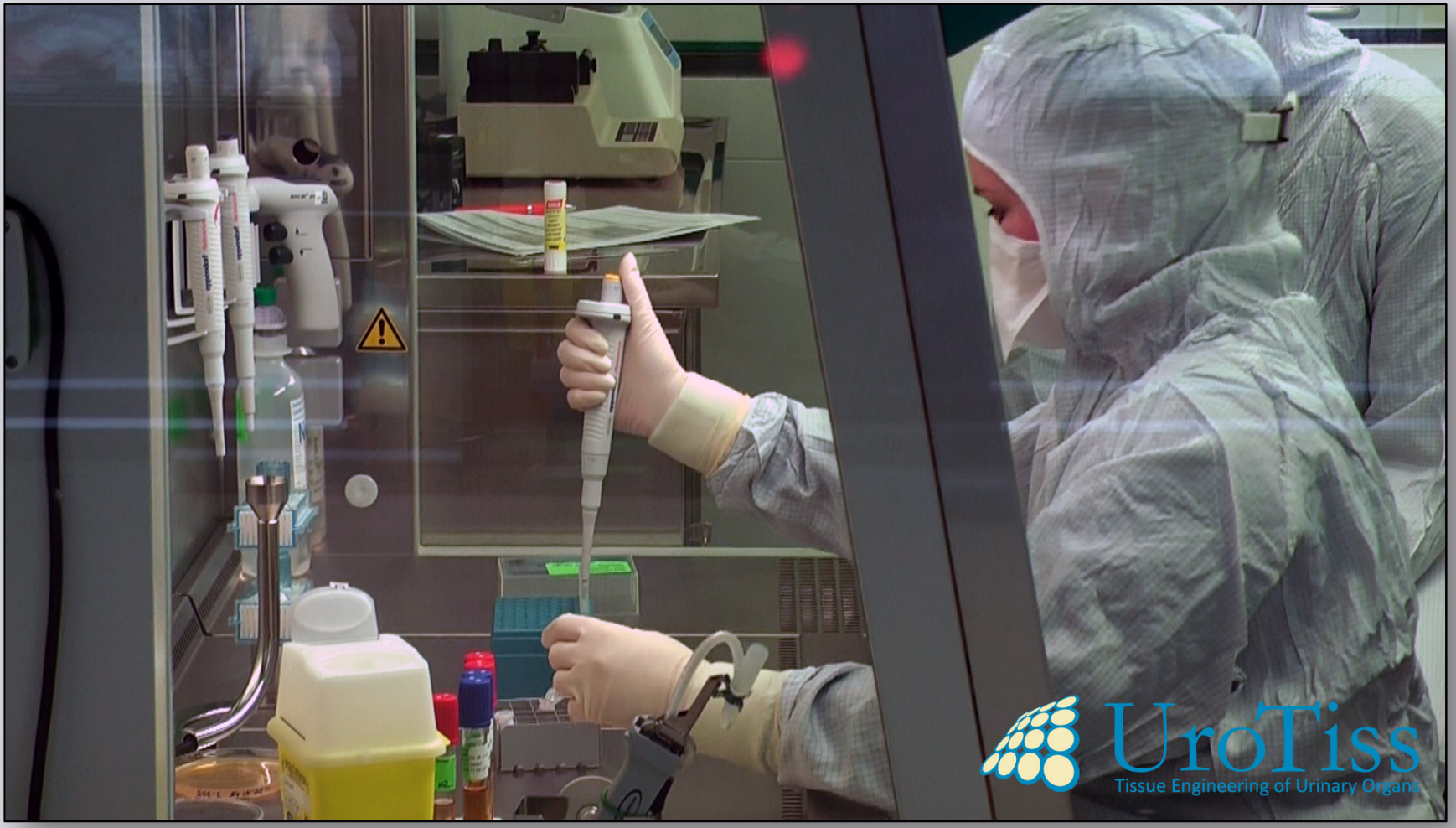

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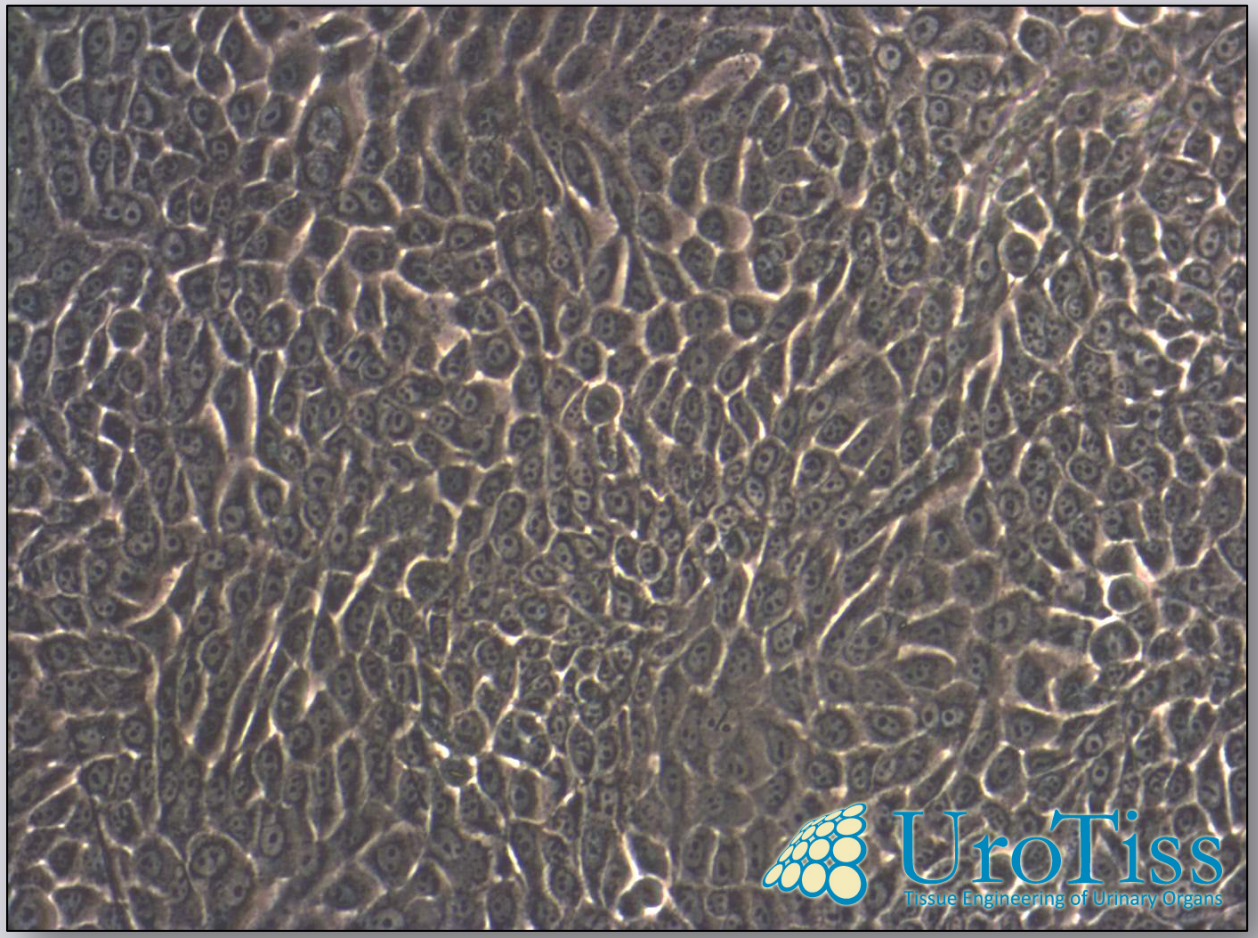

Cells were expanded
and cultured on the surface of a biocompatible scaffold.

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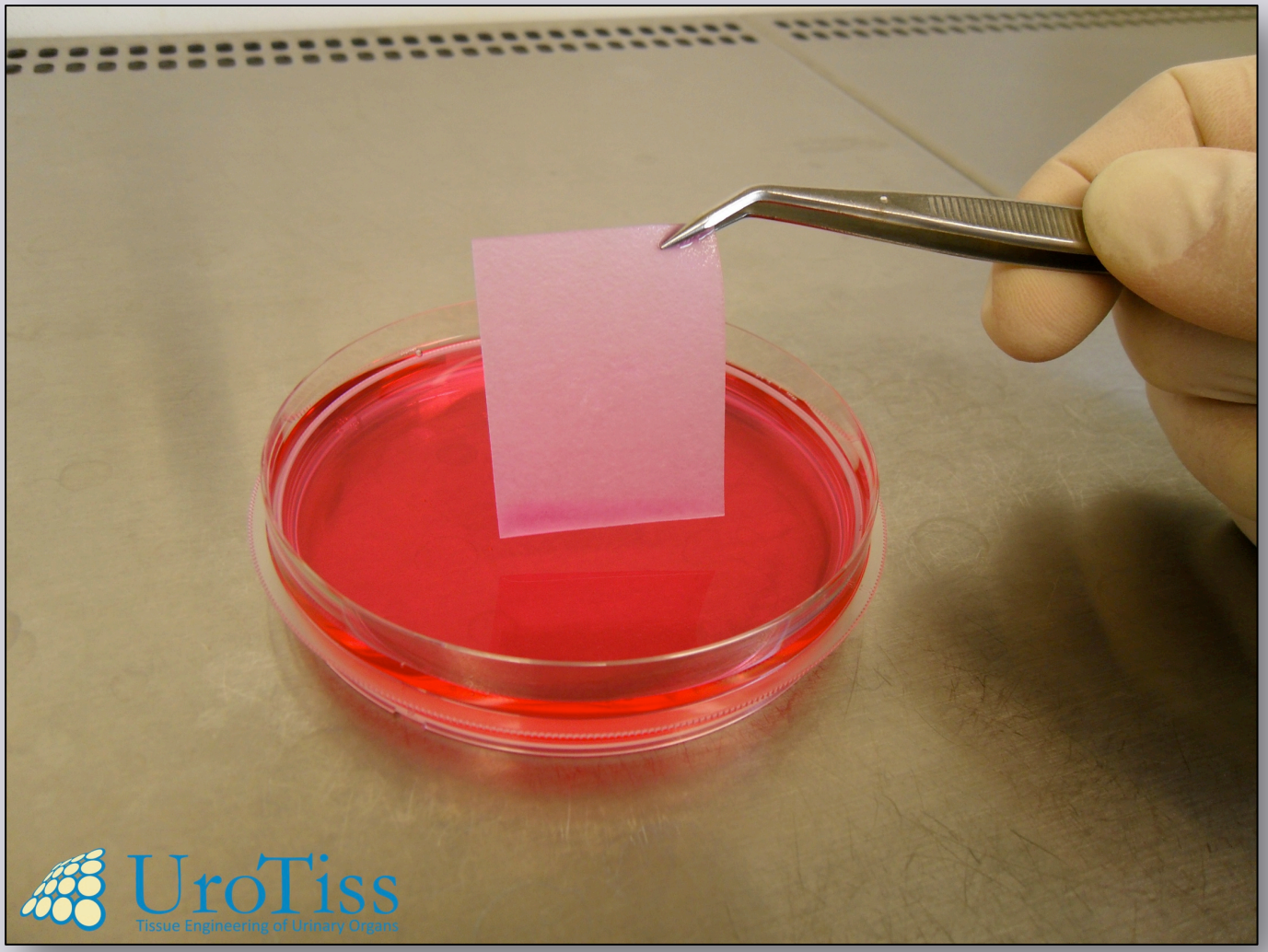

3 weeks later

48 hours for transplant

Step 3

Surgical transplant

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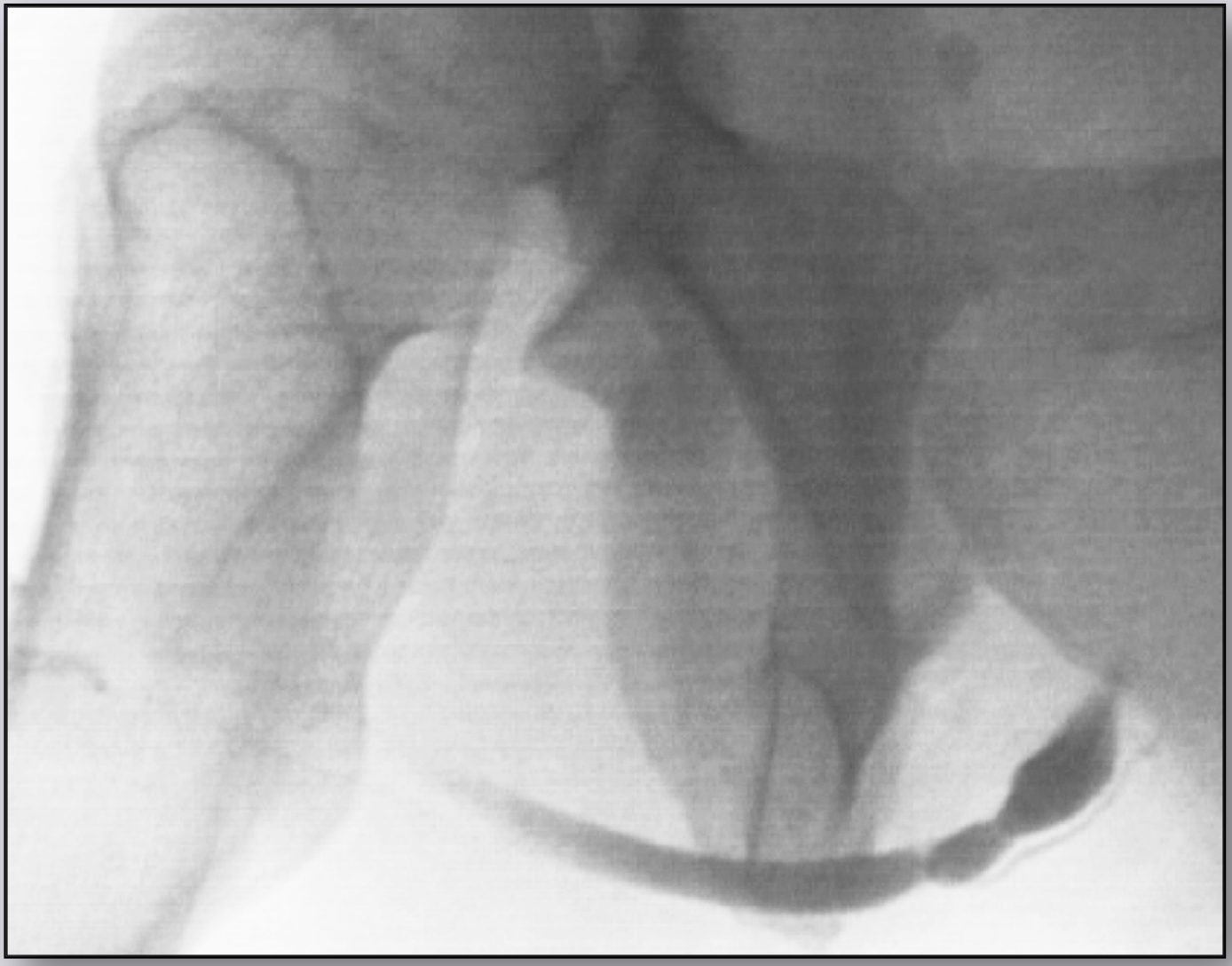
Pre-operative retrograde urethrography



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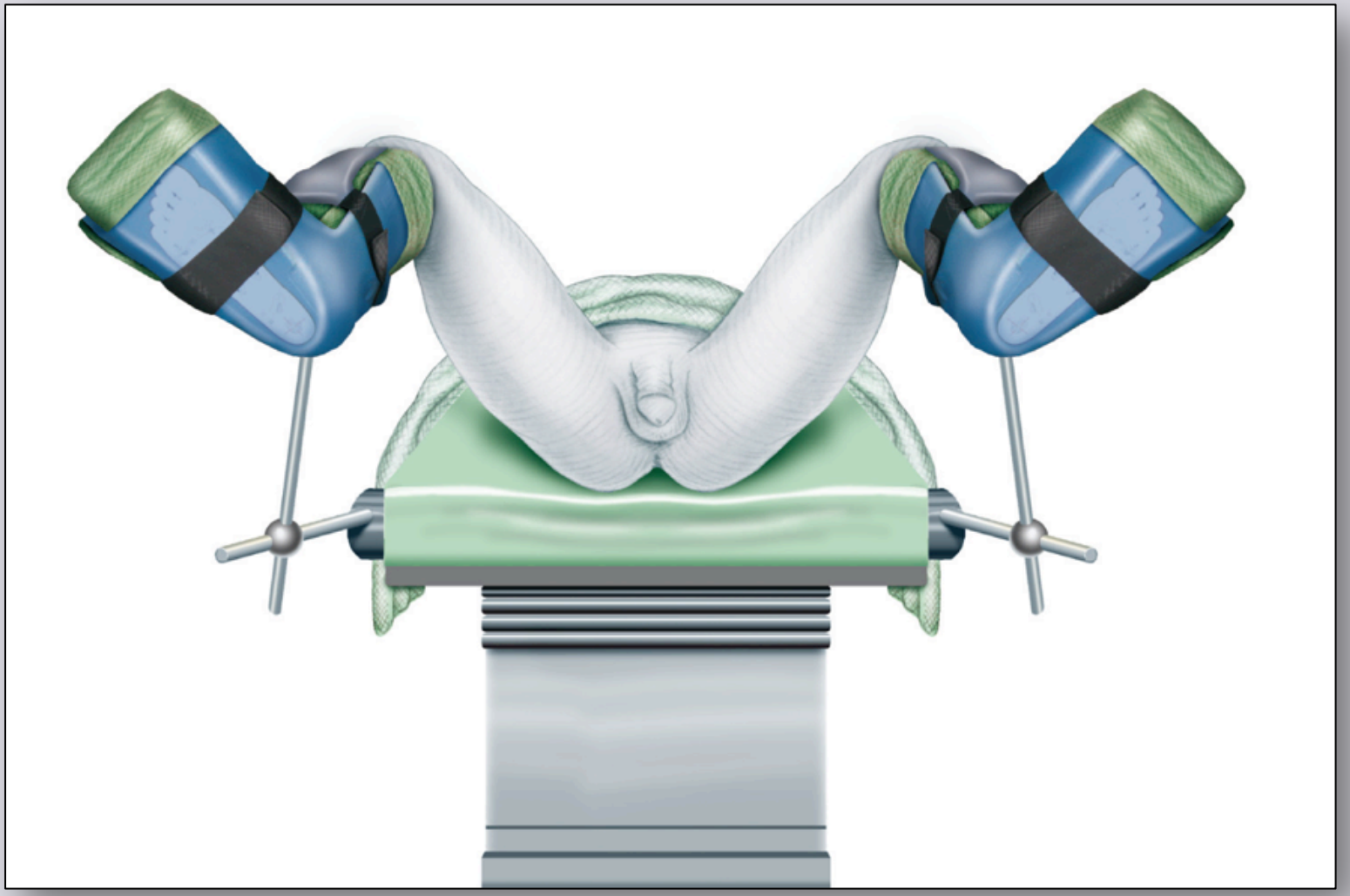
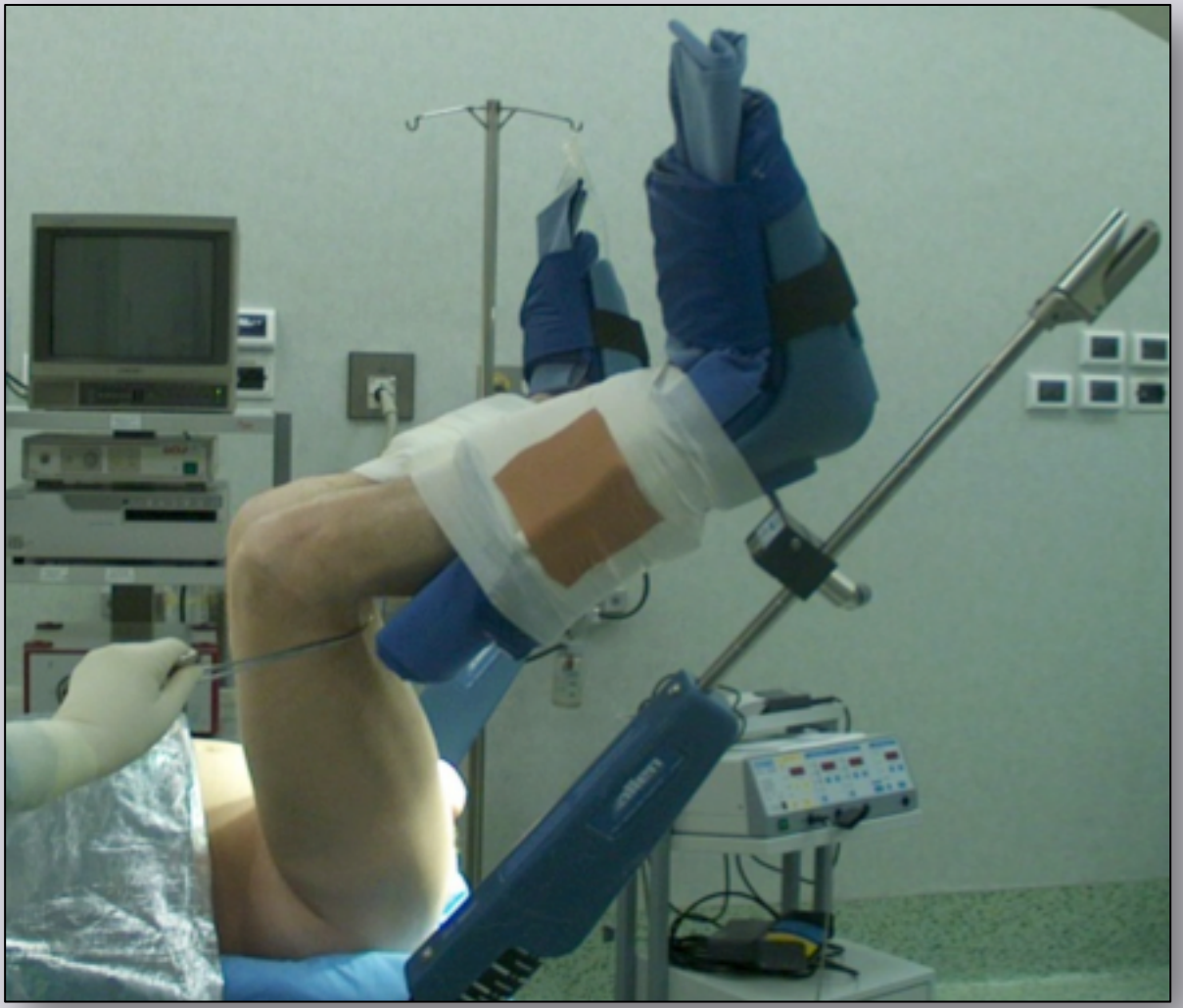
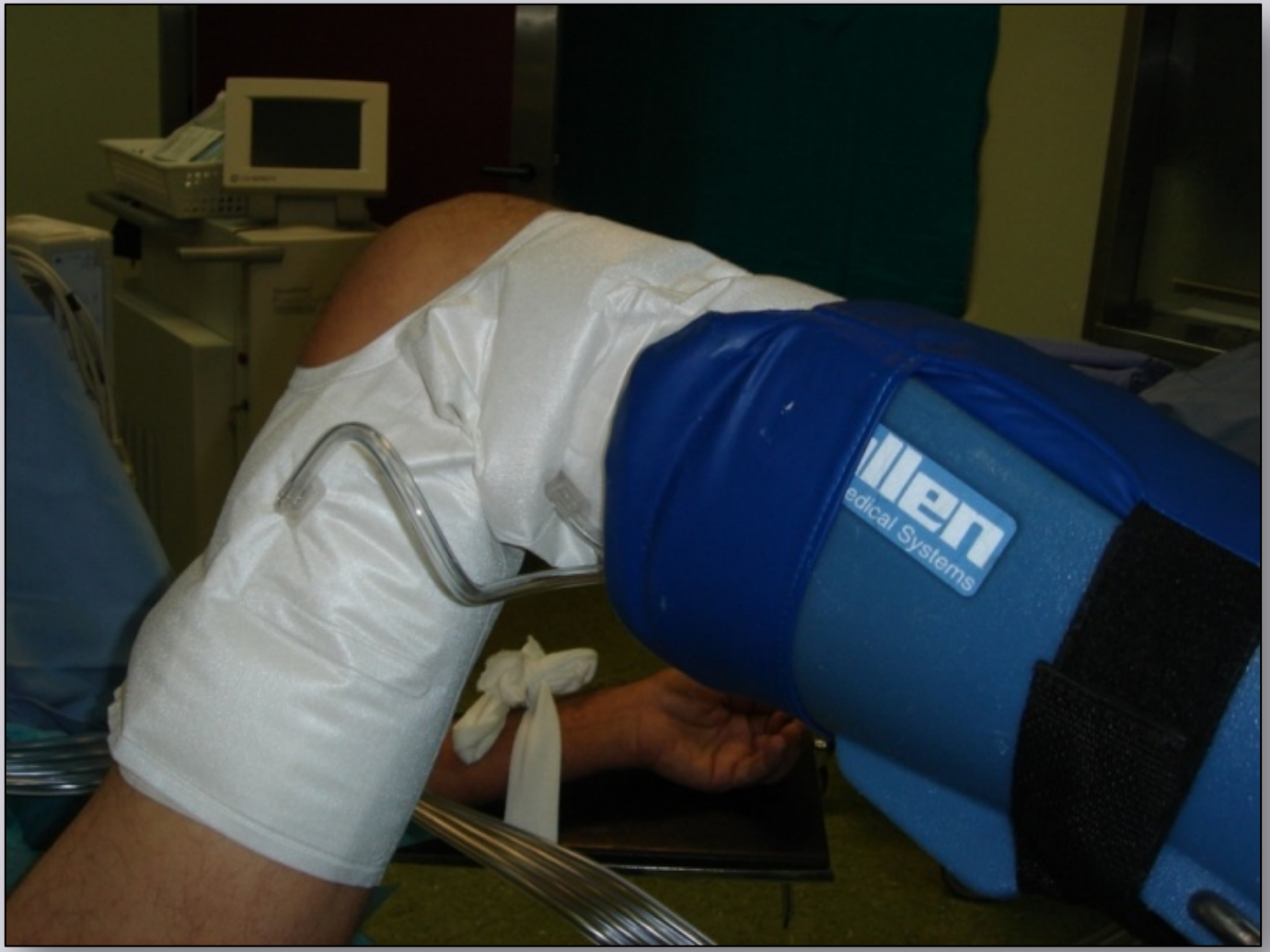


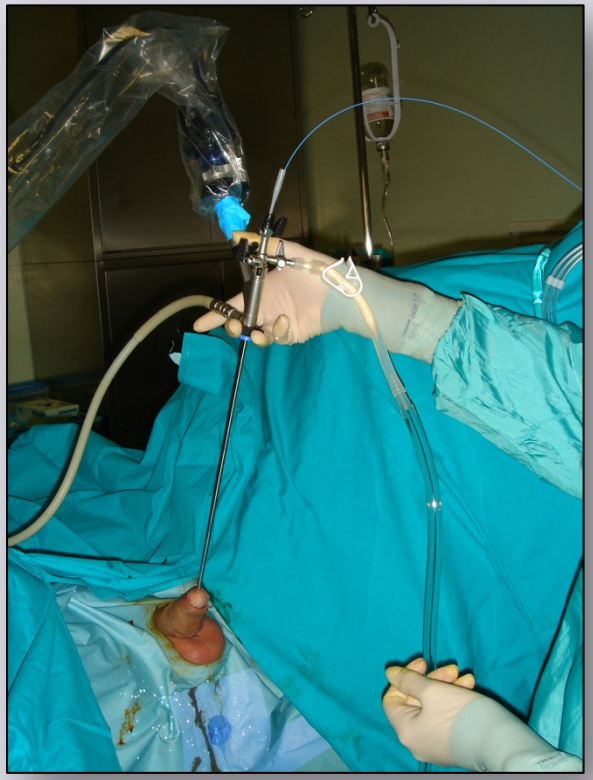
Simple lithotomy position



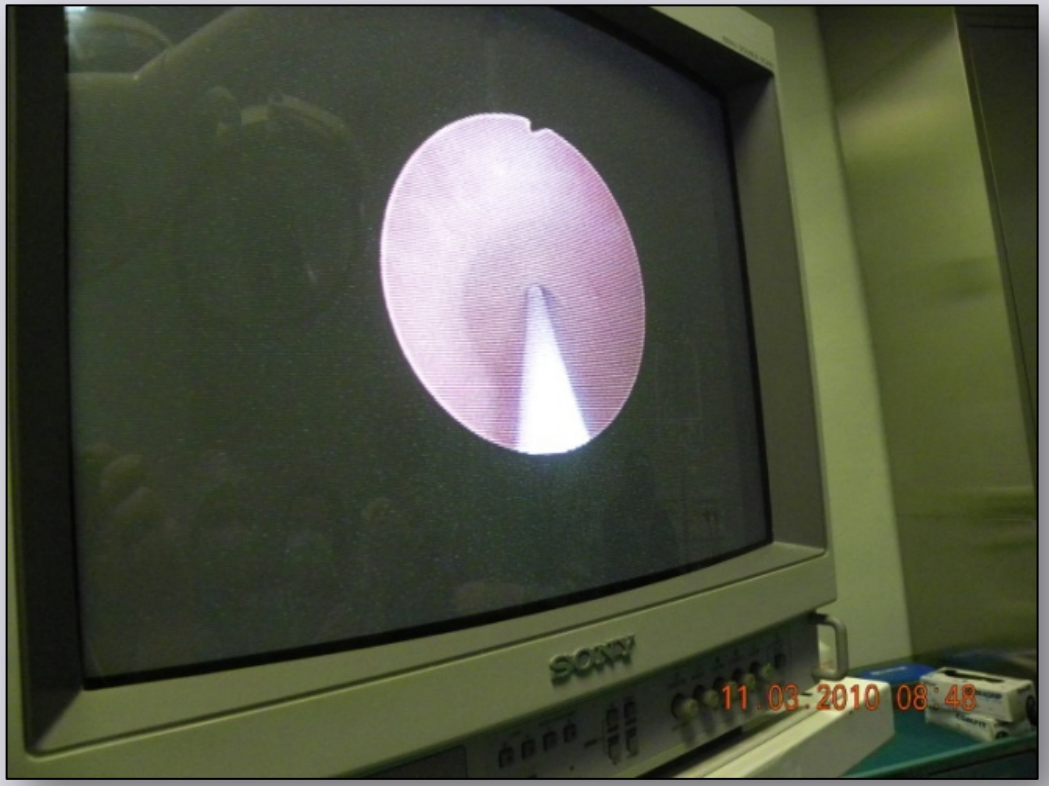
Allen stirrups



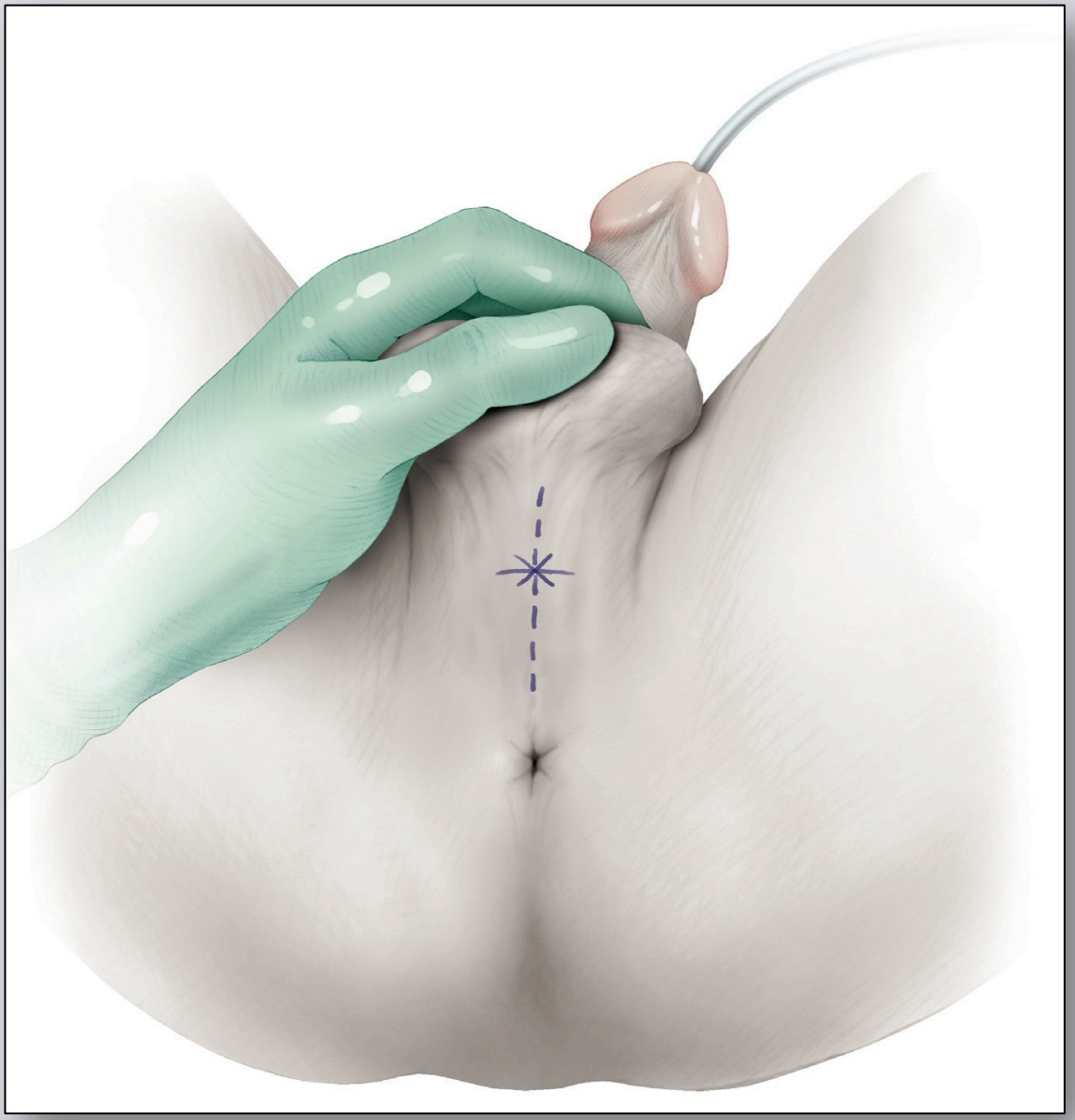
Sequential inflatable compression sleeves



Pre-operative urethroscopy



Insert Sensor 3 Fr. guidewire



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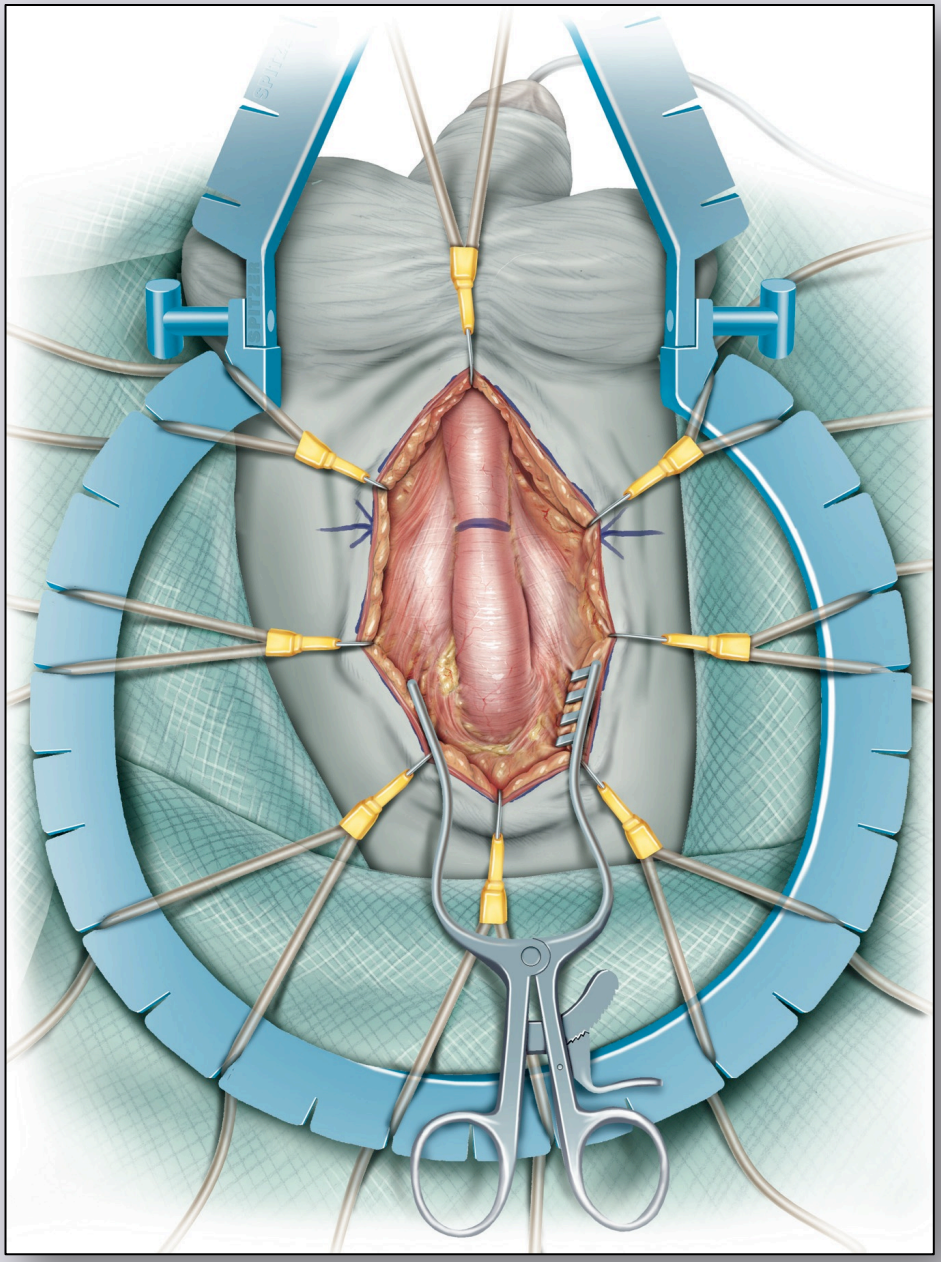

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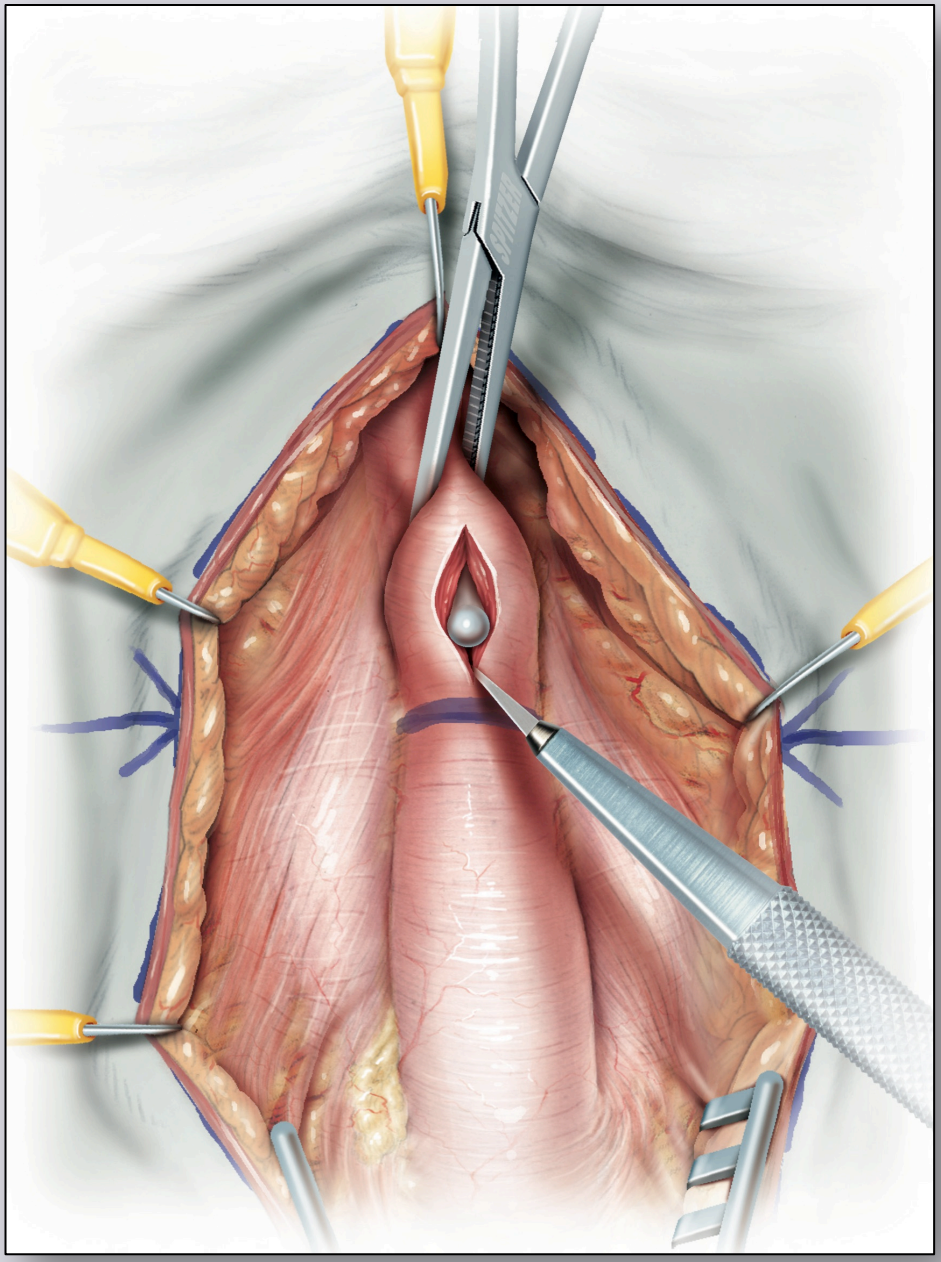

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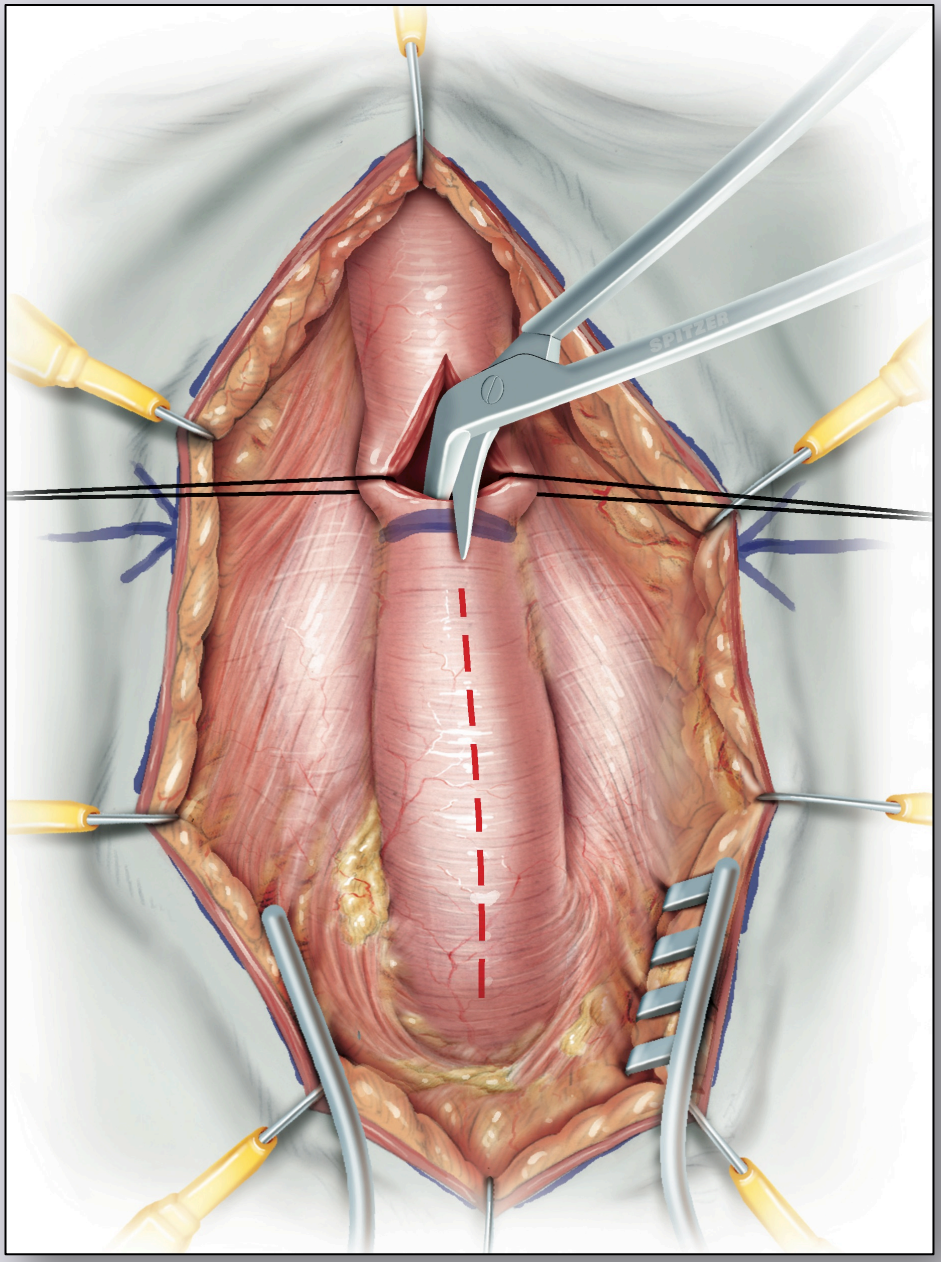

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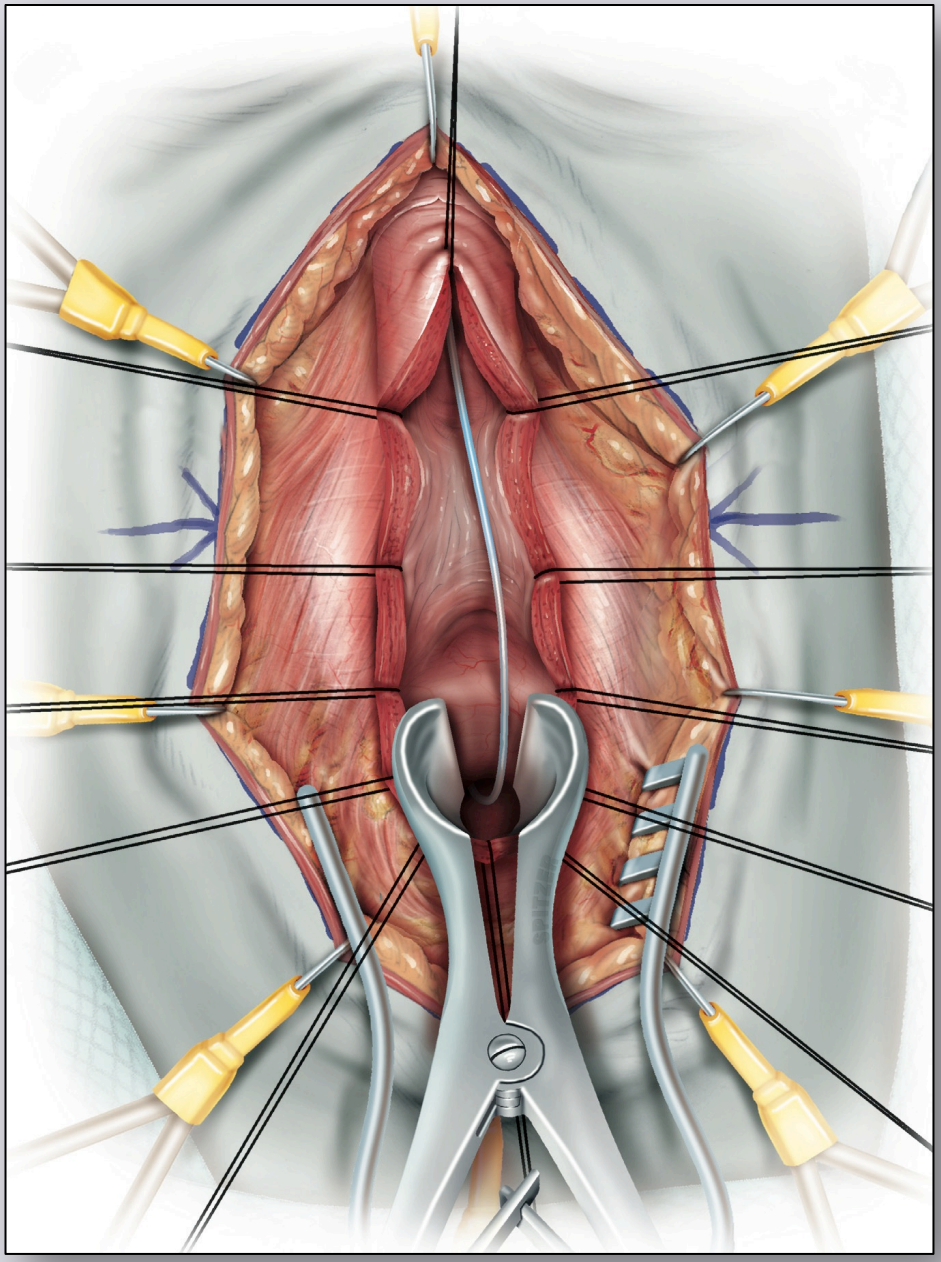

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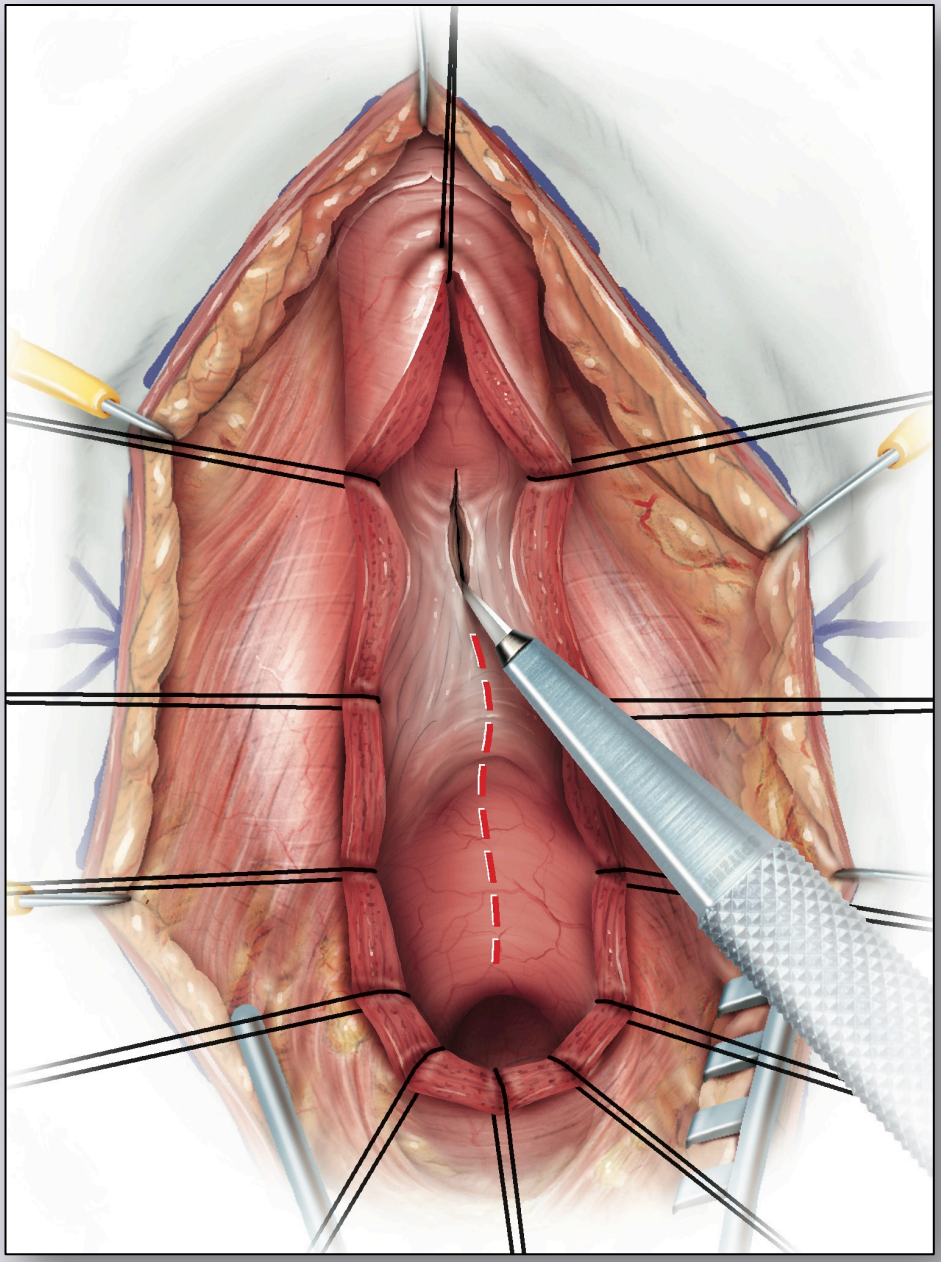

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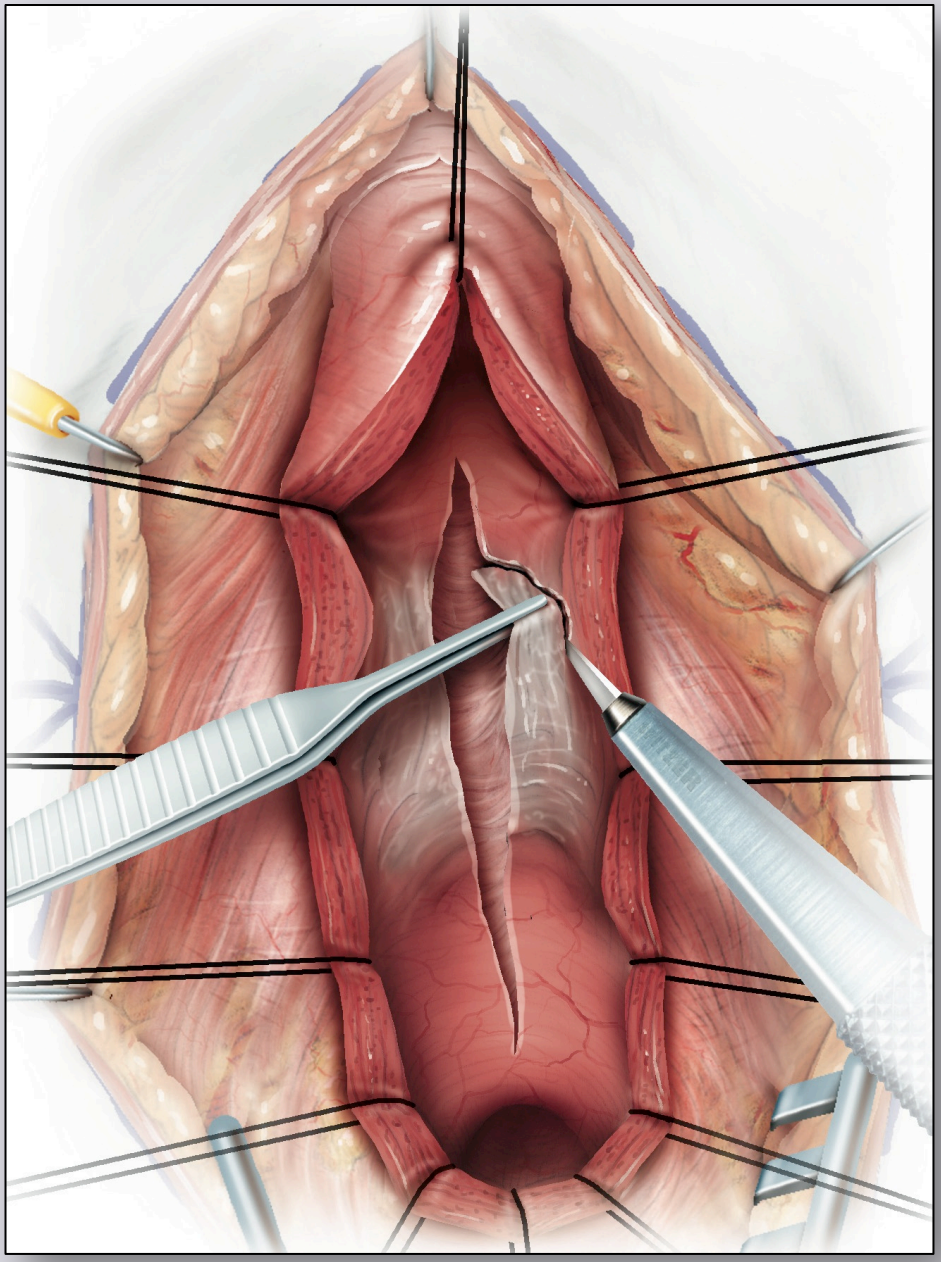

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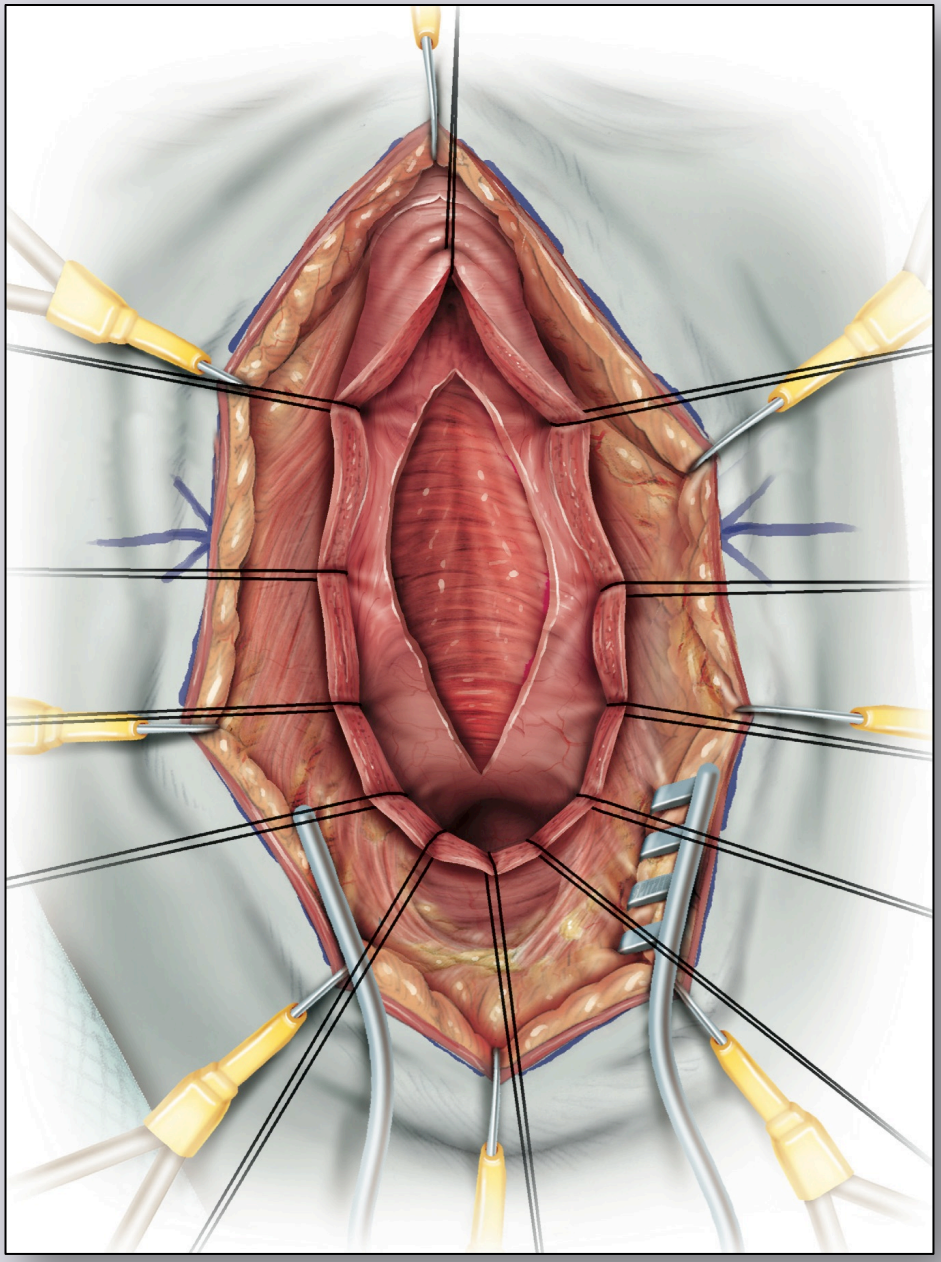

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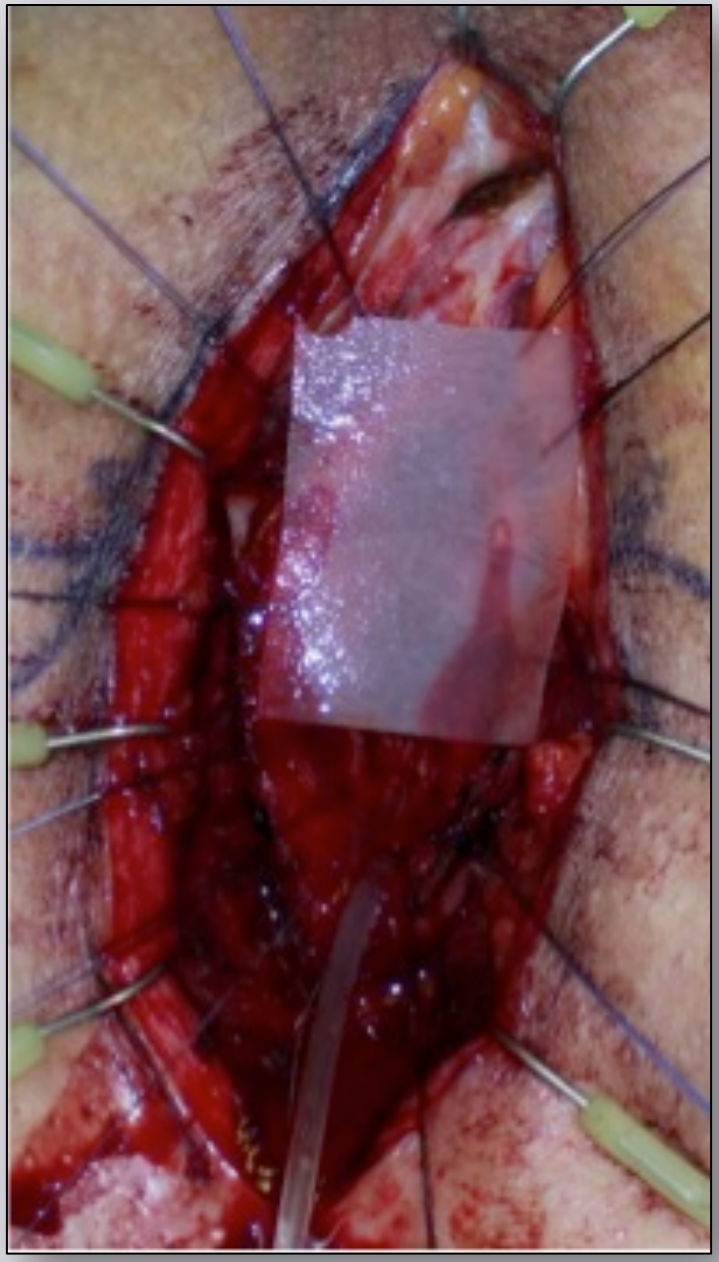

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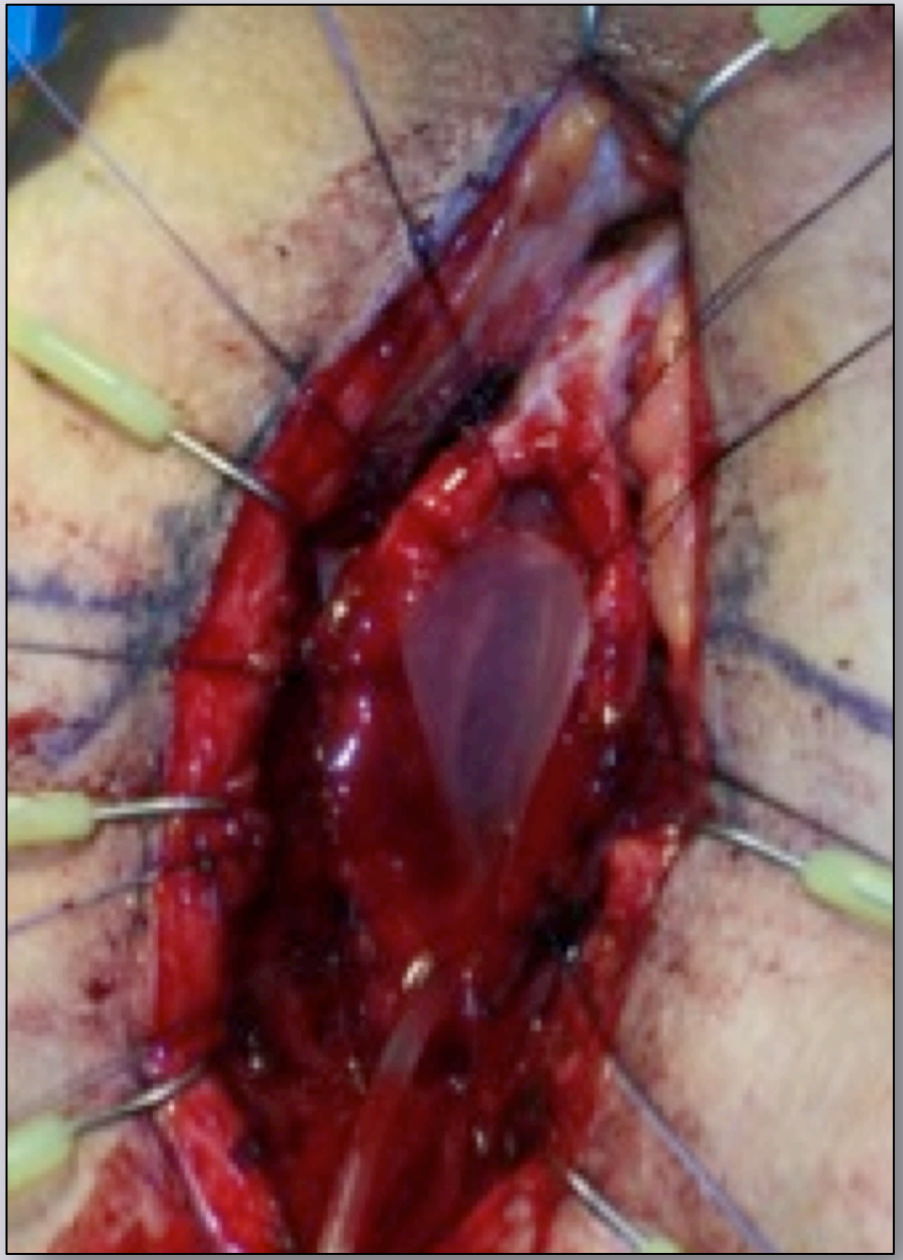

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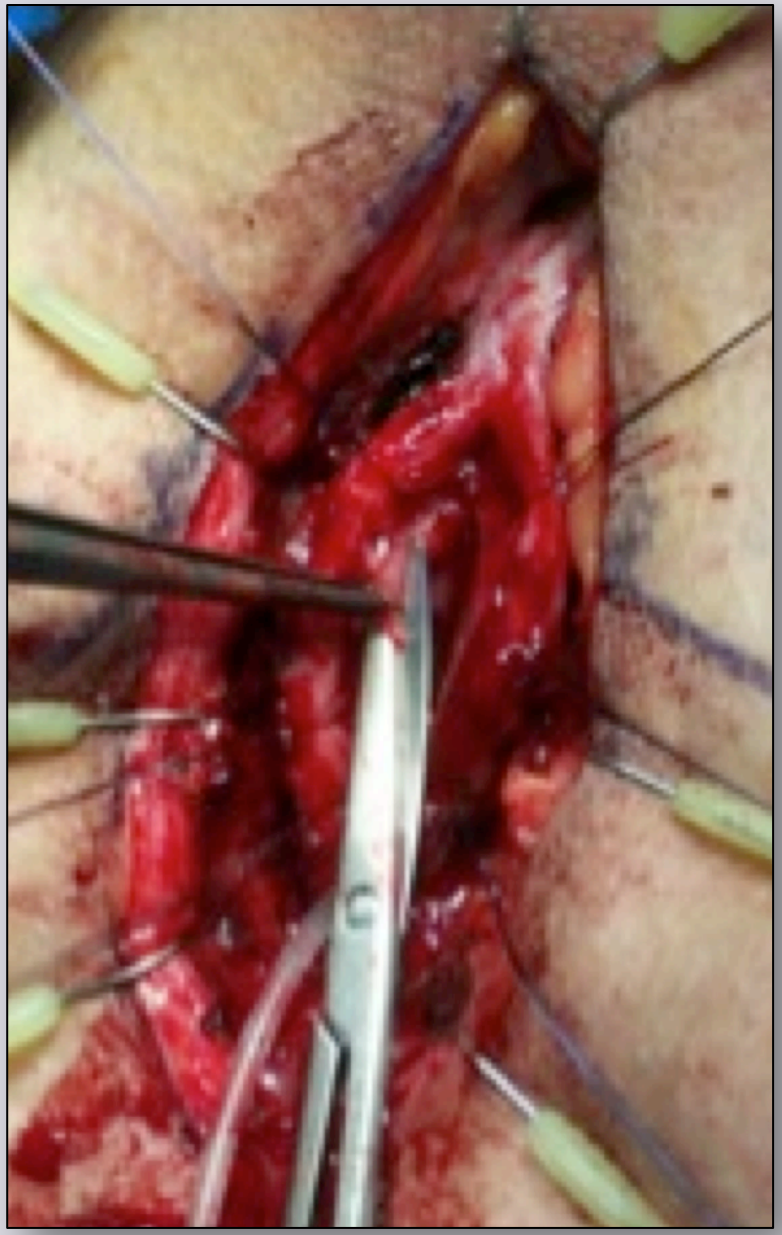

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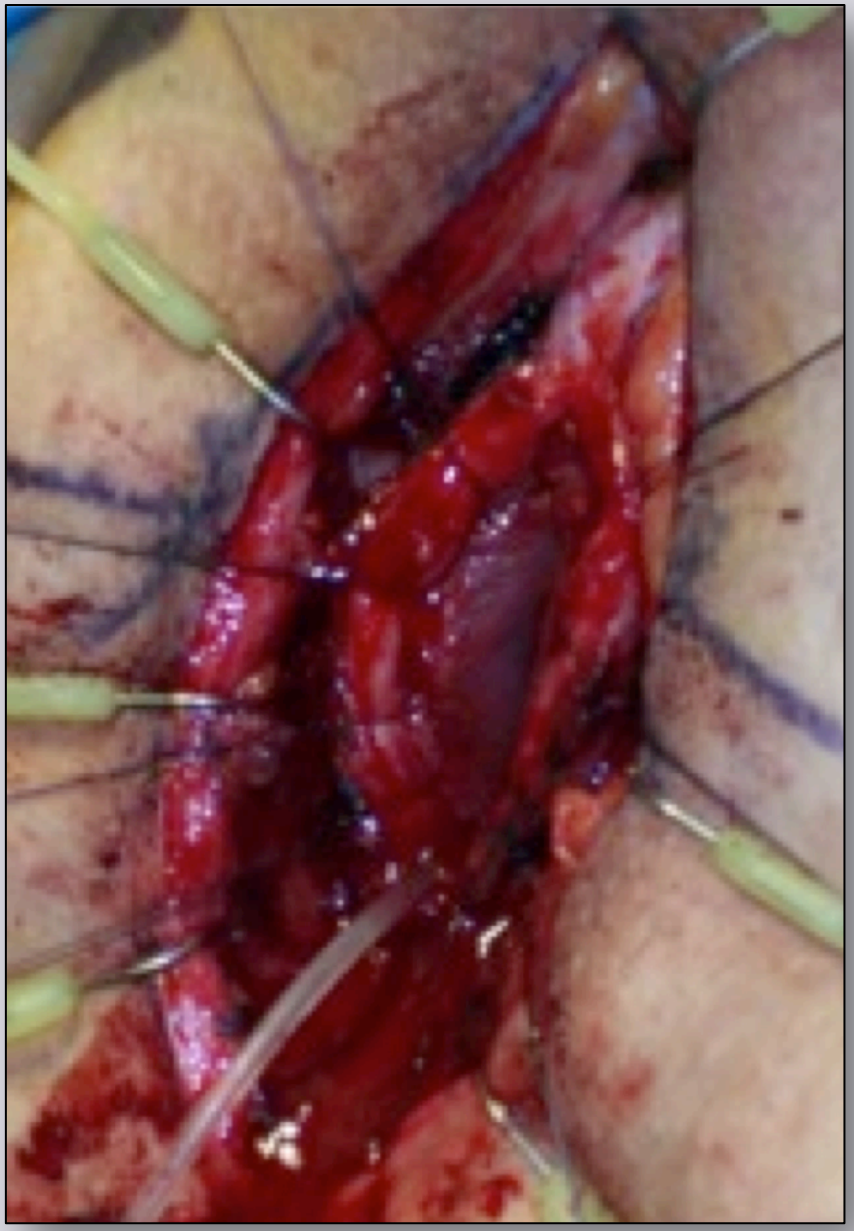

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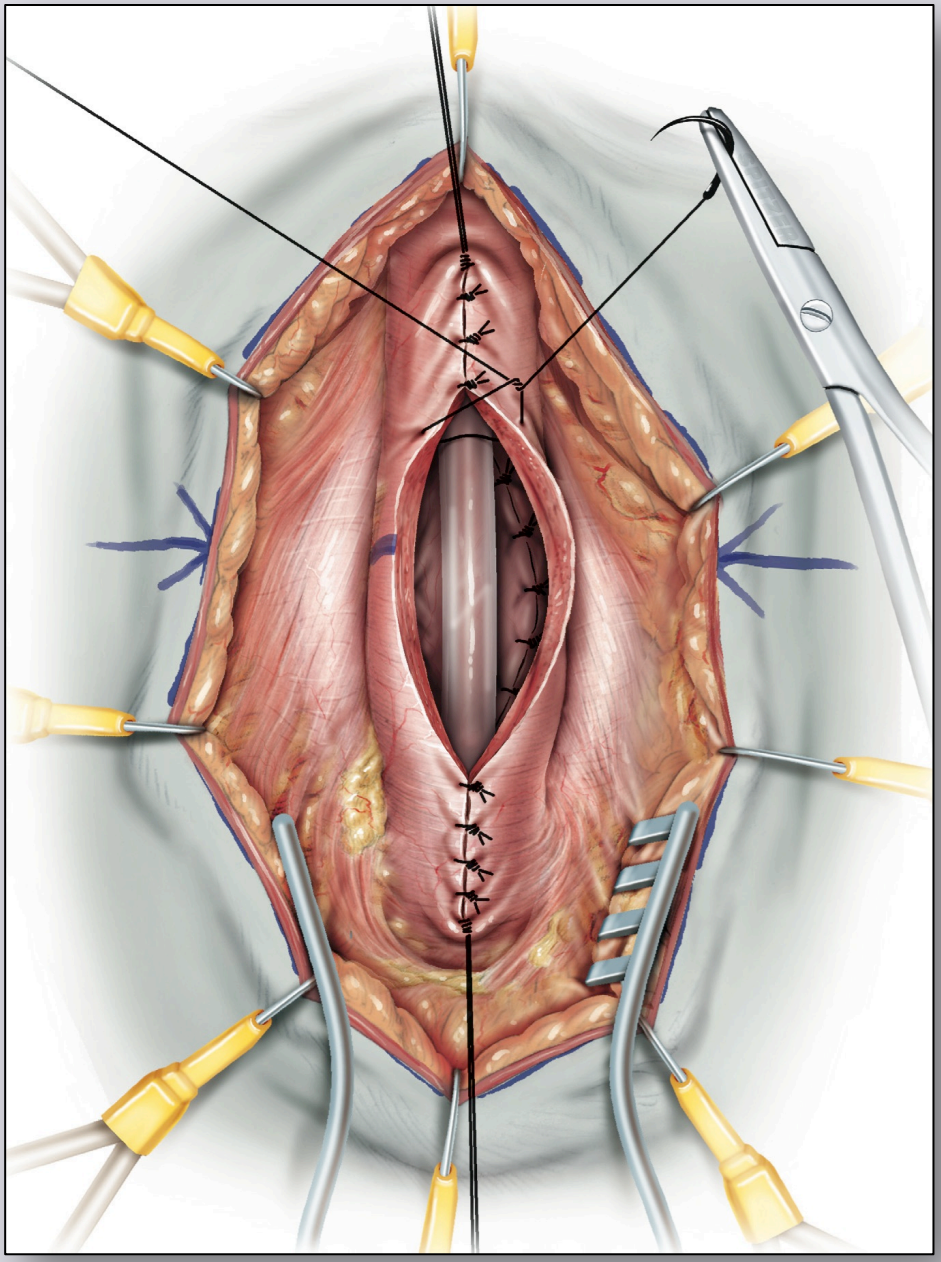

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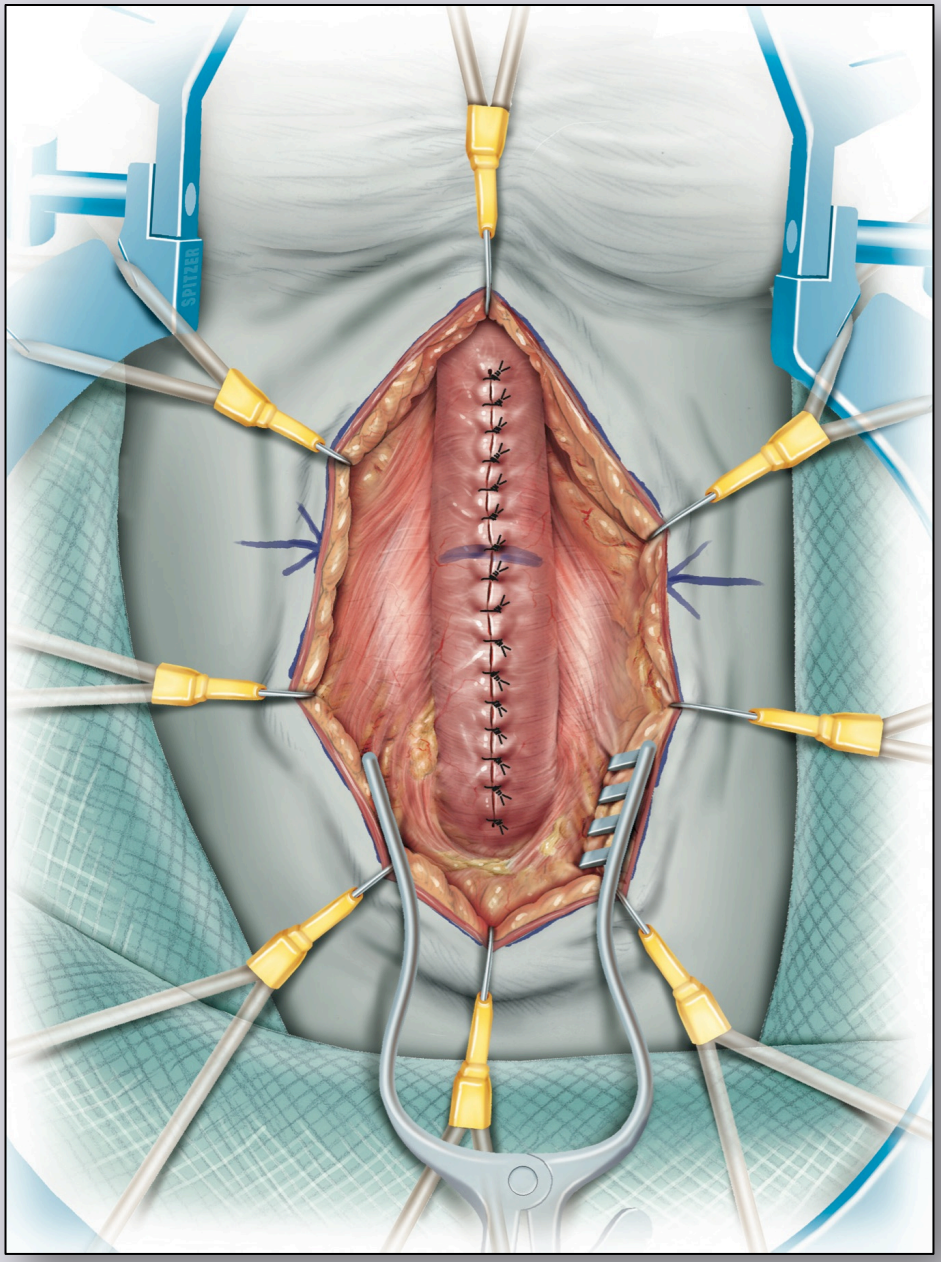

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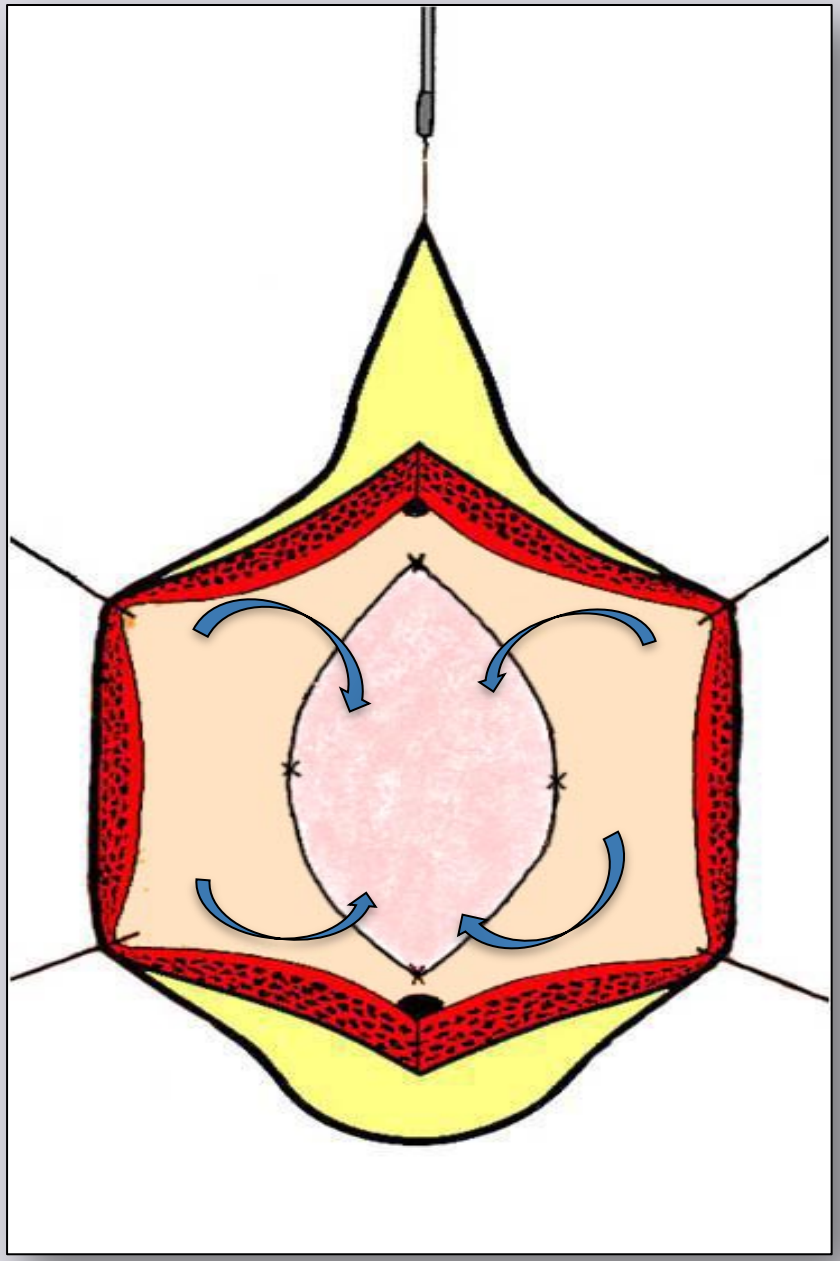

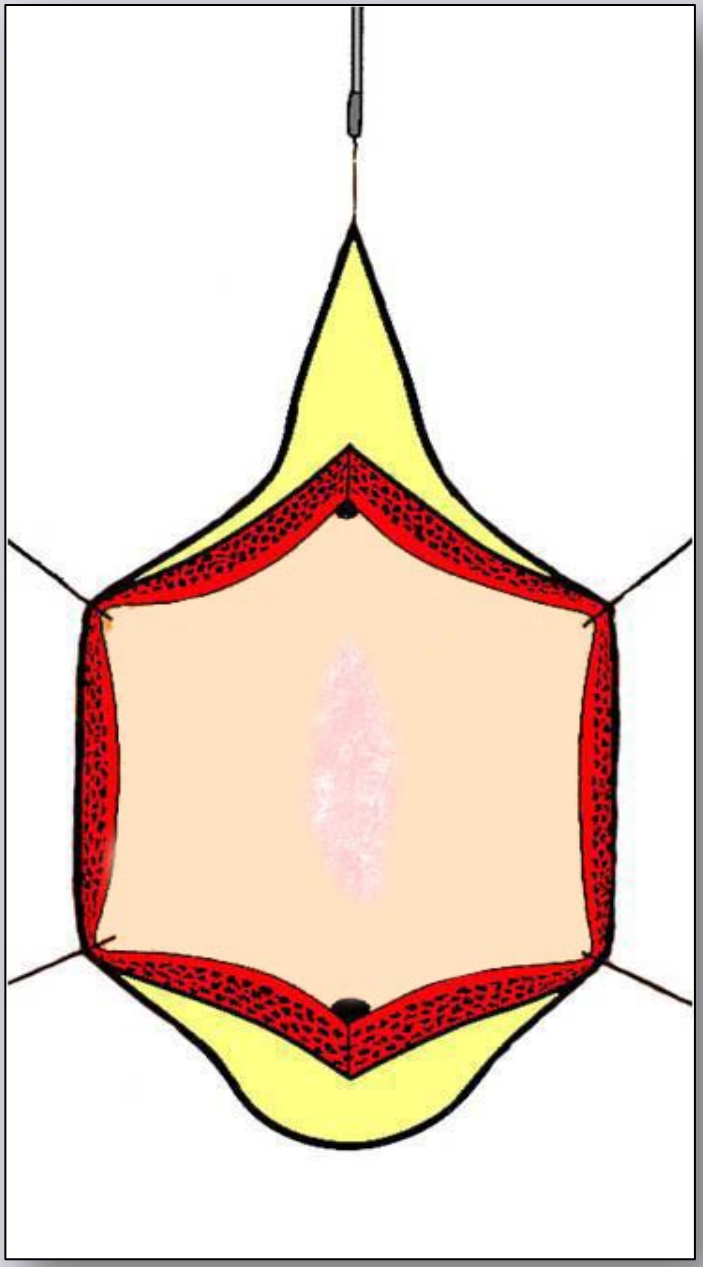

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Preliminary series of patients

12 patients

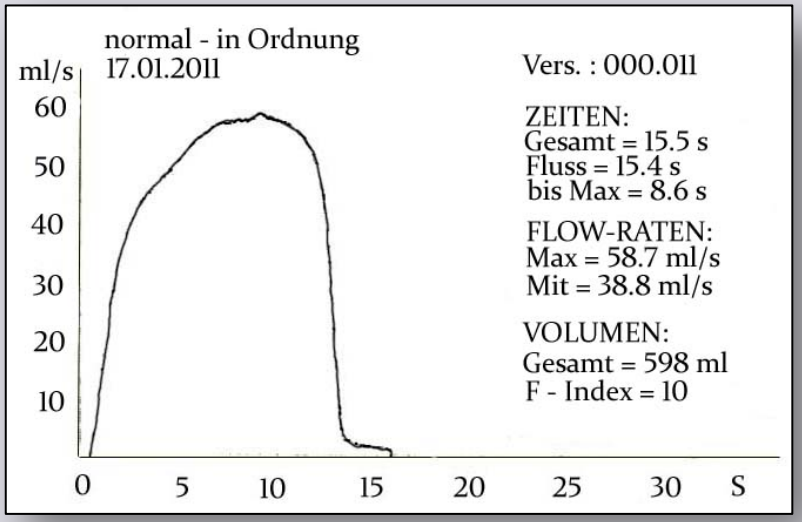
Bulbar urethral stricture

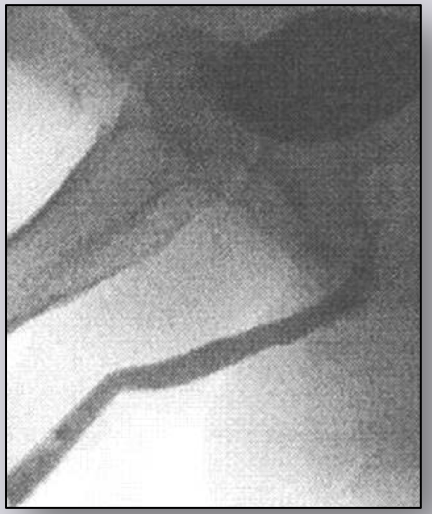
- ✓**Mean age:** 53 years (range 28 – 75)
- ✓**Median follow-up:** 18 months (range 12 – 28)
- ✓**Median stricture length:** 4 cm (range 2 –6)

Preliminary results at short-term follow-up (median: 18 months)

Ouf of 12 patients, 10 (83%) do not require further urethral manipulation, after the

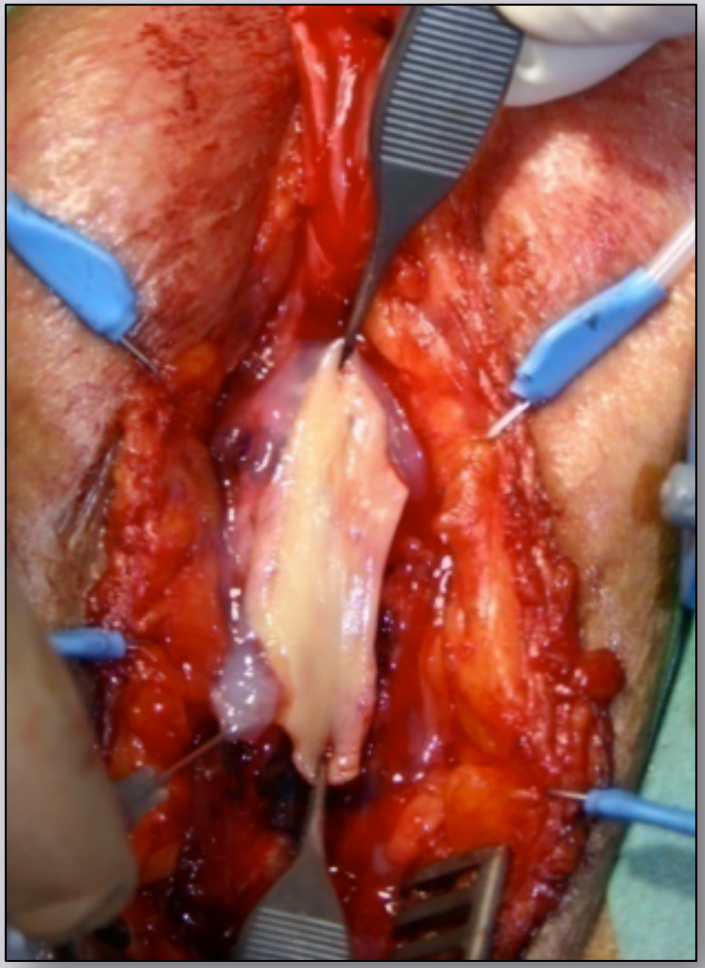
MukoCell's transplantation into the bulbar urethra



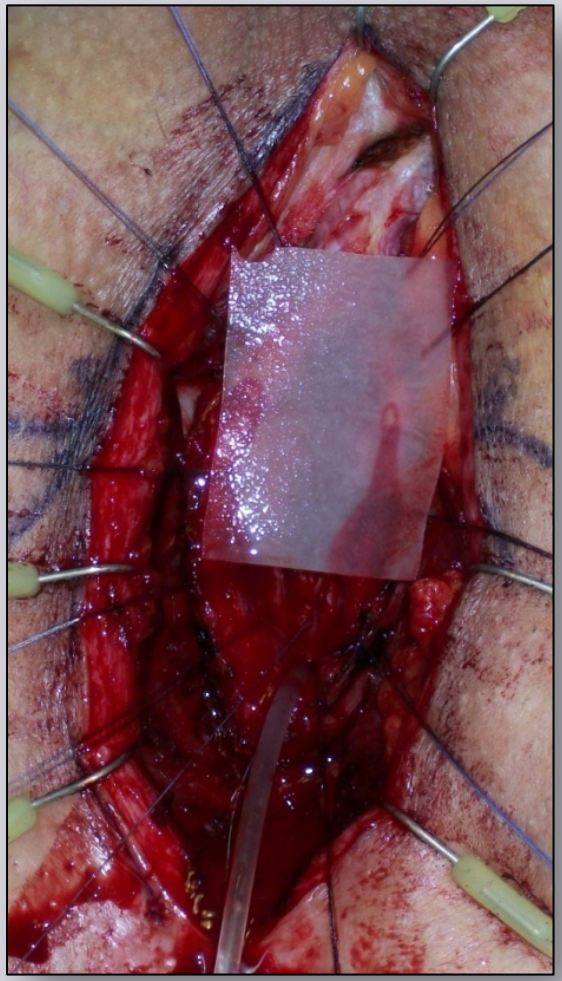


The mean Qmax increased from 3 ml/sec preoperatively to 20 ml/sec postoperatively

Our preliminary experience



Oral mucosa



Tissue engineered oral mucosa

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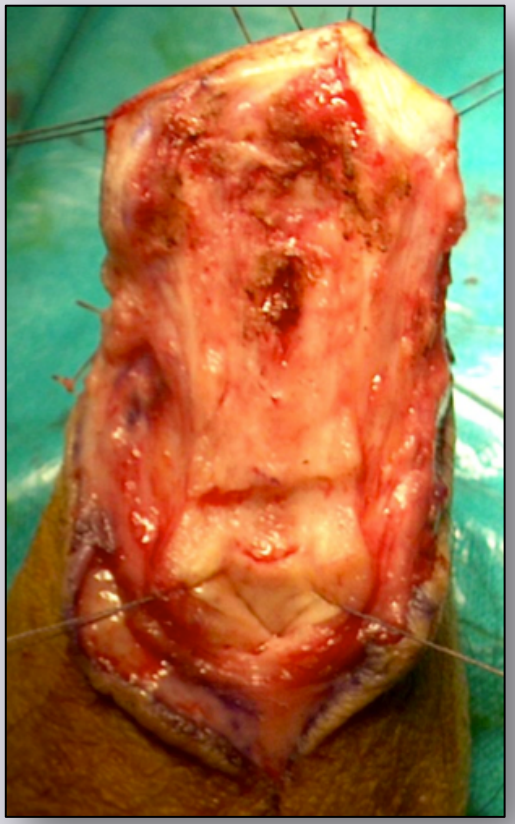
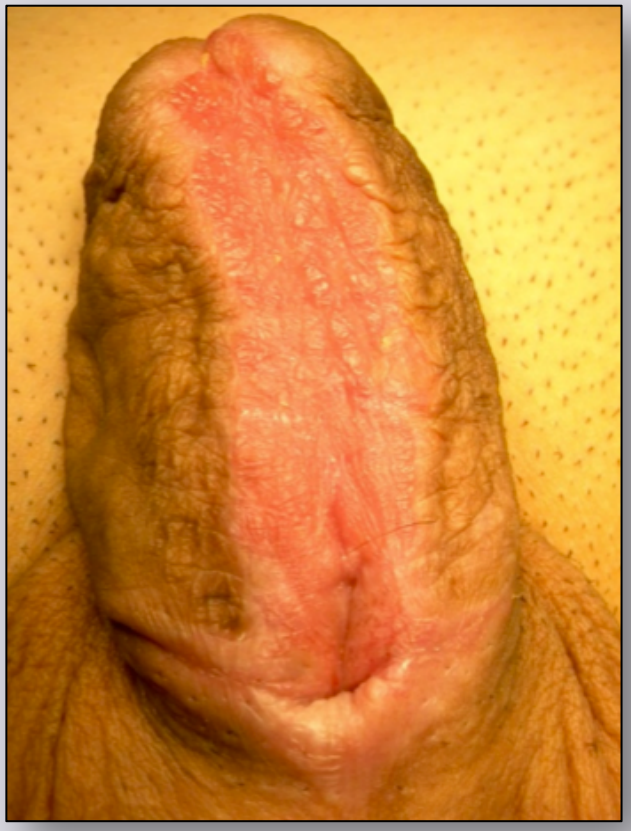
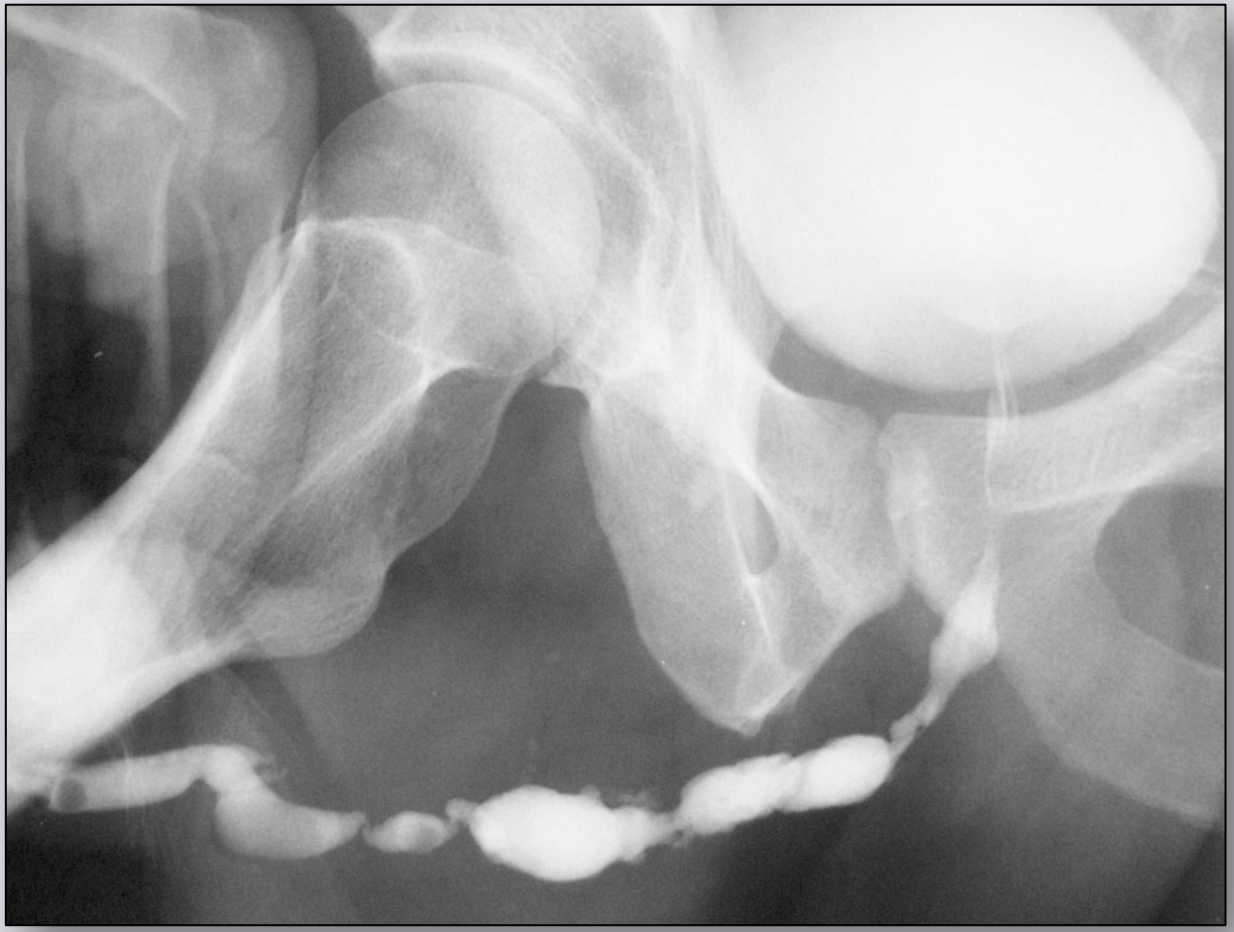
Our preliminary experience





Is tissue engineered oral mucosa adaptable for any type of urethroplasty ?

Our preliminary experience



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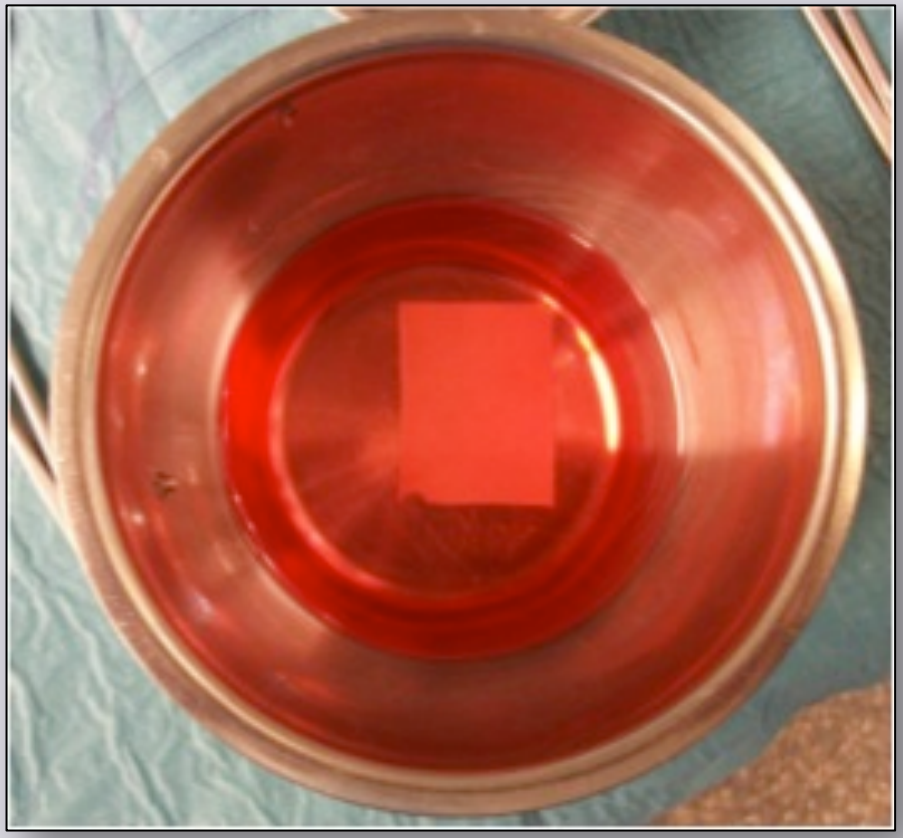
Our preliminary experience



The use of tssue engineered oral mucosa is not a simple surgical procedure and should be performed only in a Centre of excellence for urethral surgery

Take home message:

It is not the end line of the long history of urethral reconstruction, but the first step for a new future of urethral surgery

Limitations of this study

- **Small 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**

For more information about MukoCell manifacturing or if you are interested in developing this technology in your country please contact Dr. Gouya Ram-liebig at:

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