6th Confederación Americana de Urologia Residents Education Programme (CAUREP)

2 October 2019, Buenos Aires, Argentina

EAU Education Office

esu eau European School of Urology

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6th Confederación Americana de Urologia Residents Education Programme (CAUREP)
2 October 2019, Buenos Aires, Argentina

Chairs:
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EAU/ESU: J. Palou, Barcelona (ES)

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T. Cai, Trento (IT)
C. Chapple, Sheffield (GB)
J. Palou, Barcelona (ES)
J. Walz, Marseille (FR)

CAU Faculty:
P. Palma, Campinas (BR)
F. Rodriguez (MX)
R. Sotelo, Los Angeles (US)
J. Gutiérrez, Winston Salem (US)

07.00 – 07.05 Welcome
J. Gutierrez, CAU Secretary General
J. Palou, ESU Chairman

Functional urology
07.05 – 07.30 Management of female stress urinary incontinence
C. Chapple, Sheffield (GB)
07.30 – 08.00 Overactive bladder: Concept and practical management
P. Palma, Campinas (BR)
08.00 – 08.30 Let´s clarify underactive bladder
C. Chapple, Sheffield (GB)

Prostate cancer
08.30 – 09.00 Fusion biopsy: Where are we?
J. Walz, Marseille (FR)
09.00 – 09.30 Castrate resistant prostate cancer update
F. Rodriguez (MX)
09.30 – 10.00 Clinical implications on daily practice of MRI of the prostate
J. Walz, Marseille (FR)

10.00-10.30 Coffee break

Laparoscopic surgery
10.30 – 11.00 Limits of radical kidney laparoscopic surgery
J. Palou, Barcelona (ES)
11.00 – 11.30 Trocar position in kidney and pelvic laparoscopic/robotic surgery according to anatomy
R. Sotelo, Los Angeles (US)
11.30 – 12.00 Laparoscopic/robotic cystectomy, outcomes
J. Palou, Barcelona (ES)
12.00 – 12.30 Laparoscopic/robotic management of urinary fistula
R. Sotelo, Los Angeles (US)

12.30-14.30 Lunch and Industry sponsored symposium

Urinary tract infection

14.30 – 15.00 Antimicrobial resistance: Be careful!
T. Cai, Trento (IT)

15.00 – 15.30 Antibiotic prophylaxis in endoscopic urological surgery
J. Gutiérrez, Winston Salem (US)

15.30 – 15.55 Update in the diagnosis and medical treatment of acute cystitis and pyelonephritis
T. Cai, Trento (IT)

15.55 – 16.00 Closure and Farewell
J. Gutiérrez, Winston Salem (US)
J. Palou, Barcelona (ES)

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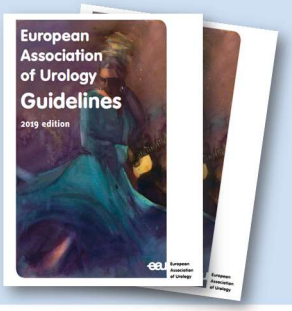
58 endorsements of National Societies



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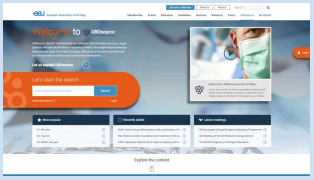

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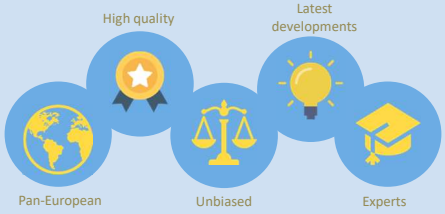

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European experts of laparoscopic & endoscopic surgery

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Webinars

We do: e-Courses

Primary Urethral Carcinoma
EAU Guidelines on Primary Urethral Carcinoma. New!

Men's health
EAU Guidelines on Men's Health

Thromboprophylaxis
EAU Guidelines on Thromboprophylaxis.

Prostate Cancer
Metastatic Prostate Cancer
EAU Guidelines on Prostate Cancer

Bladder Cancer
Non-Muscle-Invasive Bladder Cancer
EAU Guidelines on Non-muscle-invasive Bladder Cancer. New!

Renal Cancer
EAU Guidelines on Renal Cell Cancer

Urolithiasis
Introduction to upper urinary tract endoscopy for stones
EAU Guidelines on Urolithiasis

Functional Urology
Overactive bladder: mechanisms and management
Overactive bladder: onabotulinumtoxinA as treatment
Risk profile-oriented management of BPE/LUTS

We do: Webinars

Every month 30-minute webinar

International Key Opinion Leaders

16 recorded webinars

We do: Surgical Education

Online Programmes:

- Endoscopic Stone Treatment (EST)
- European training in Basic Laparoscopic Urological Skills (E-BLUS)
- Robotics in Urology

Hands-on Training:

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- Diagnostics and follow-up
- Functional Urology
- Endoscopy

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- European School of Urology's flagship teaching programme
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- Comprehensive update, overview of modern urological practice
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We do: Meetings

URO Berlin Skills Teaching and Training (UROBESTT)

3-day programme for young urologists with

- Challengers session
- Hands-on training
- Tips and tricks
- Clinical cases

We do: Meetings

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3 step programme for 3rd year residents:

- Lectures
- Hands-on training
- Case discussion

We do: Courses at National Society's Meetings

20+ Courses
around the World

We do: Masterclasses

We do: ESU courses at EAU Section meetings

In close collaboration with the various EAU Sections, the ESU organizes many courses during the Section meetings

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Educational activities are developed in close conjunction with the ESU

Research in subspecialist fields in urology is stimulated and executed

We do: Scholarships

The European Urological Scholarship Programme (EUSP) offers 5 different programmes:

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Only EAU members are eligible to apply for scholarships!

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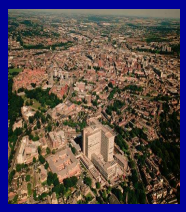
Contemporary Management of Stress Urinary Incontinence in the Female



Christopher Chapple
Sheffield Teaching Hospitals
NHS Foundation Trust
UK

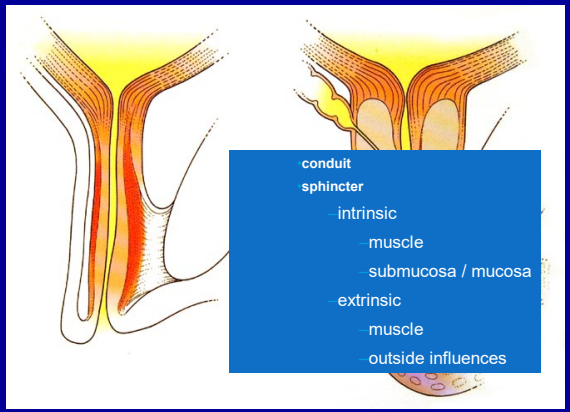
CAU 2019

The University Of Sheffield.
Sheffield Hallam University
Sheffield Teaching Hospitals NHS

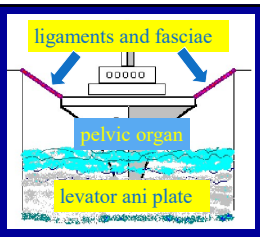
European Association of Urology

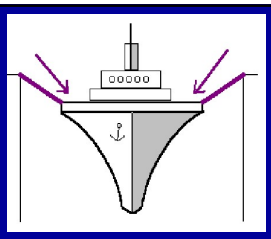
Disclosures

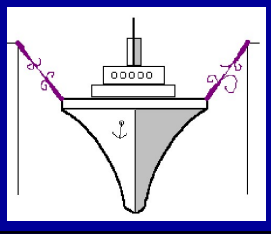
Nil relevant



- conduit
- sphincter
  - intrinsic
    - muscle
    - submucosa / mucosa
  - extrinsic
    - muscle
    - outside influences





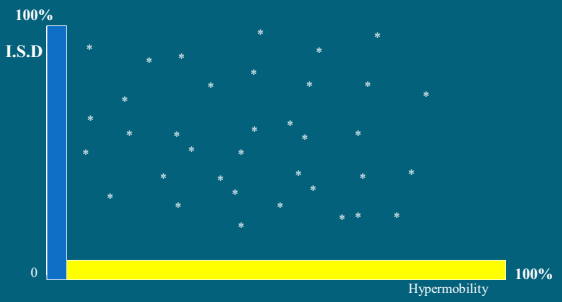


Interplay between muscles/nerves and connective tissue

Pelvic floor function

- Support of pelvic organs
- Resist increases in abdominal pressure
- Recoil when stretched

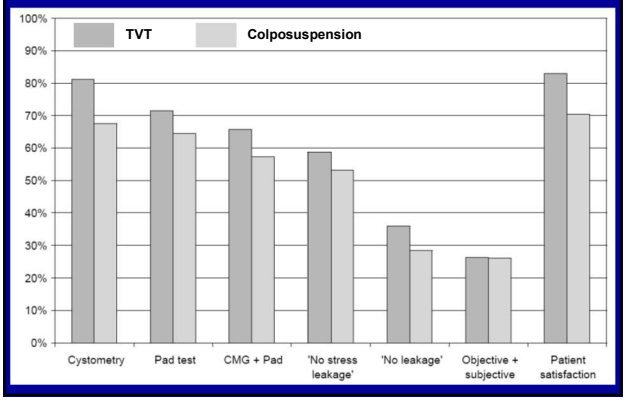
Classification of patients according to their physiopathology



Outcome assessment

- Incontinence episode frequency (IEF)
- Objective cure/improvement rate:
  - Pad test of qualified leakage
- Subjective cure/improvement rate:
  - Woman's perception of cure (dry) or improvement
- Urodynamic cure?
  - Absence of leakage during Valsalva manoeuvre and repeated coughing
  - Significant improvement in MUCP

Cure rates: different definitions



Match the therapy to the patient


Int Urogynecol J (2005) 16: 171–173
DOI 10.1007/s00192-005-1300-y

EDITORIAL

Linda Brubaker · Bob Shull

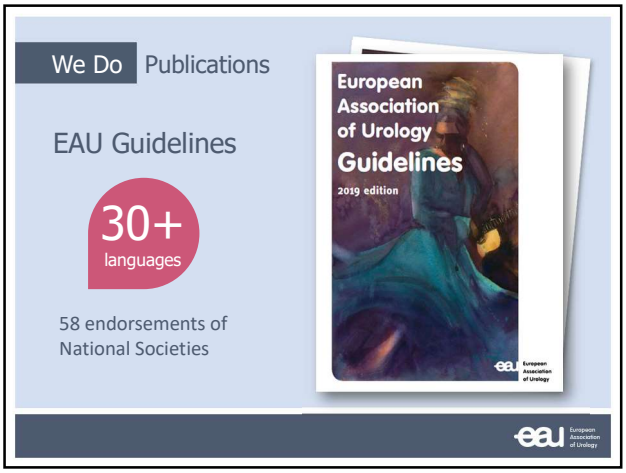
EGGS for patient-centered outcomes

Patient-selected goals: A new perspective on surgical outcome

Eman A. Elkadry, MD,[a] Kimberly S. Kenton, MD,[a] Mary P. FitzGerald, MD,[a] Susan Shott, PhD,[b] and Linda Brubaker, MD[a]

Maywood and Chicago, Ill

EXPECTATIONS
GOAL SETTING
GOAL ACHIEVEMENT
SATISFACTION



Treatment of SUI

- Conservative treatment:
  - Pelvic floor muscle training (PFMT)
  - Electrical Stimulation
  - Devices
  - Pharmacotherapy
- Surgical treatment:
  - Urethral bulking agents (Injectables)
  - Colposuspension
  - Sling procedures:
    - Classic
    - Tension-free vaginal tape (TVT).....

Conservative therapies

- General (medications/co-morbidities)
- Lifestyle Modification
- Containment
- Behavioural and Physical therapies

Recommendation	Grade

Behavioural / Physical Therapies

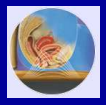
- Bladder training
- PFMT
- Biofeedback
- Electrical Stimulation
- Magnetic stimulation
- PTNS

Behavioural and physical therapies

Recommendation	Grade
Offer supervised PFMT lasting at least 3 months, as first line therapy to women with SUI or MUI	A
PFMT programme should be as intensive as possible	A
Consider using biofeedback as an adjunct	A

Electrical and Magnetic stimulation

Recommendation	Grade
Do not offer E Stim with surface electrodes (skin, vaginal ,anal) alone for the treatment of UI	A
Do not offer Magnetic stimulation for the treatment of UI or OAB	B



Devices

- External collection devices
- Devices which support the bladder neck
  - Efficacious
- Extraurethral occlusive devices
- Intraurethral devices

Insufficient evidence of long-term efficacy, safety, cost-efficacy and improvement in QoL

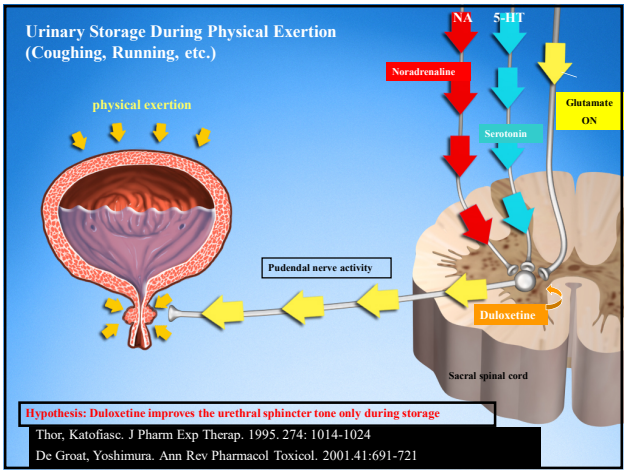
Wilson PD, Bø K et al. 2nd ICI, Paris, 2002;571-624

Pharmacotherapy

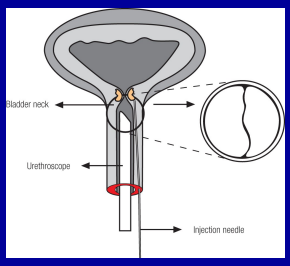
Off-label use	On-label use	Side effects
Oestrogens		increased risk CV disease, breast/endometrial cancer
TCAs: -Imipramine		dry mouth, constipation, retention,orthostatic hypotension, falls
	β_2-AR agonists: -Clenbuterol (Japan)	tremor, tachycardia, headache
	α_1-AR agonists: -PPA* (Finland) -Midodrine hydrochloride (Portugal)	elevated blood pressure, palpitations, abnormal cardiac rhythms

*removed from US market due to risk of hemorrhagic stroke

Viktrup L, Bump RC. Curr Med Res Opin 2003;19:485-90



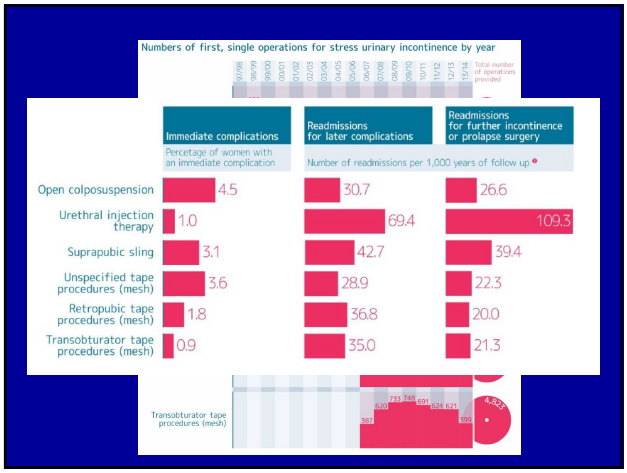
Surgery - Injectables



Limited data available

No critical appraisal possible

Pickard R et al. The Cochrane Library, Issue 1, 2004



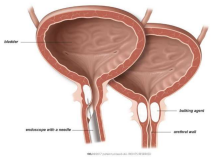
Surgery – Bulking Agents

Recommendation	Grade
Do not perform periurethral bulking injection for treatment of SUI in women who are seeking a cure	A

Guidelines

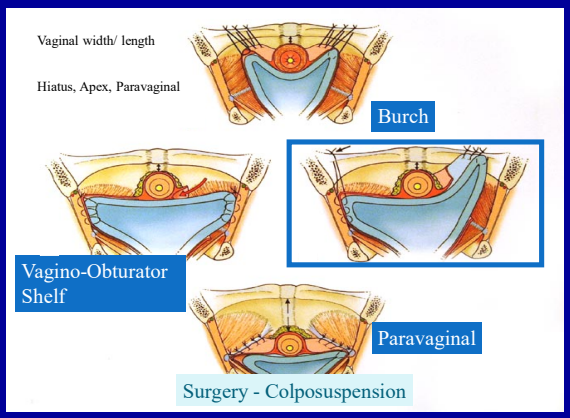
Alternatives - Bulking agents

- Periurethral bulking agents may provide short term improvement
- Repeat injections maybe necessary
- Less effective than colposuspension or PVS but less adverse events



- EAU Guidelines on Urinary Incontinence
- Kirchin V, Page T, Keegan PE, Atiemo KO, Cody JD, McClinton S, Aluko P. Urethral injection therapy for urinary incontinence in women. Cochrane Database Syst Rev. 2017

www.uroweb.org/guidelines #eauguidelines



Complications of Burch colposuspension

- Voiding dysfunction 10%
- Overactive bladder 15%
- Prolapse 10 - 25%

ICI 2012

Neurourology and Urodynamics 26:158–169 (2007)

Laparoscopic Versus Open Colposuspension for Urodynamic Stress Incontinence

Emile Tan,[1] Paris P. Tekkis,[1]* Julie Cornish,[1] Tiong G. Teoh,[2] Ara W. Darzi,[1] and Vik Khullar[2]

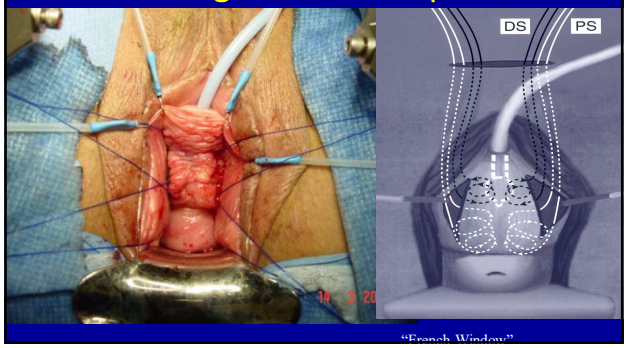
- Meta-analysis of comparative studies published between 1995 and 2006 of laparoscopic vs. open colposuspension
- 16 RCTs evaluated
- 1,807 patients, of whom 861 (47.6%) underwent laparoscopic and 946 (52.4%) open colposuspension

Similar Results

Bladder Neck Needle Suspension

- Stamey /Raz
  - Cuff complications
  - Low success
- Anterior Vaginal Wall Suspension (Zimmern)

Anterior Vaginal Wall Suspension



"French Window"

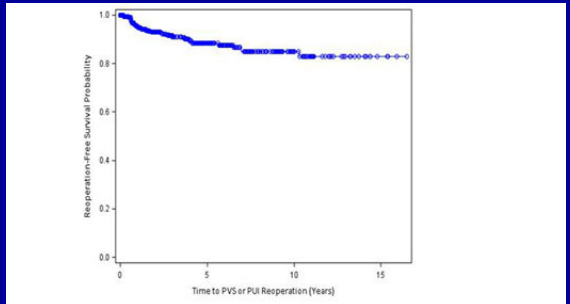


Figure 1: Kaplan-Meier Curve for Overall PVS or PUI Reoperation-Free Survival

Zimmern 2015

Alternatives – fAUS

Guidelines

- 376 AUS were implanted in 344 patients mean follow-up 9.6±4.0 yrs
- **Fully continent (no leakage) 85.6%, socially incontinent (some drops but no pad) 8.8% or incontinent (one pad or more) 5.6%**
- 10-yr device survival rates 69.2%
- Costa et al. Long-term results of artificial urinary sphincter for women with type III stress urinary incontinence. Eur Urol 2013 63:753-8
- **Continence rate is nearly 86%,** and the 10-yr device survival rate is 69%
- Phé V et al. Trends in the landscape of artificial urinary sphincter implantation in men and women in France over the past decade. Eur Urol 2013 63:407-8
- 34 patients, follow-up was 17 (12-19) years
- 26 women (74%) still had their AUS and after 20 years of follow-up, **11 women still had successful outcomes (61%).**
- Phé et al. Long-term functional outcomes after artificial urinary sphincter implantation in women with stress urinary incontinence. BJU Int. 2014 113:961-7

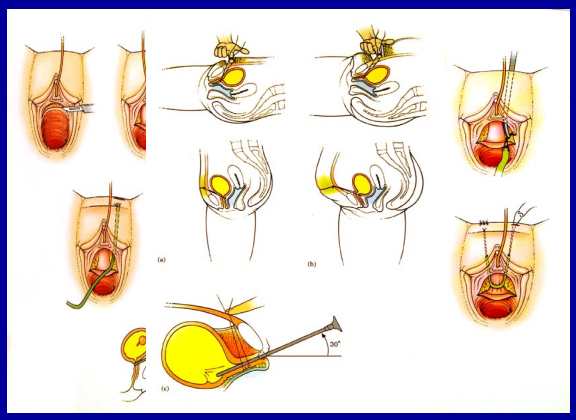
Chartier-Kastler et al. Artificial urinary sphincter (AMS 800) implantation for women with intrinsic sphincter deficiency: a technique for insiders? BJU Int. 2011 107:1618-26

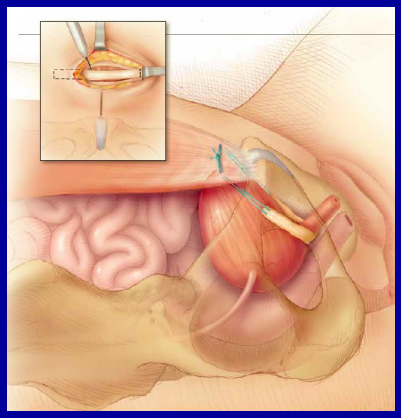
www.uroweb.org/guidelines #eauguidelines

Surgical use of biomaterials for SUI

- Synthetic meshes
  - Polypropylene mesh
    - ✔Low failure
    - ✗High complication rate
    - Mesh Erosion
    - Mesh Extrusion
    - Chronic pain
    - Infection
- Biological materials
  - Xenograft, Allograft
    - ✔Low complication
    - ✗High failure rate
    - ✗Infection risks
  - Autograft
    - ✔low failure
    - ✔Low complication rate
    - ✗Donor site morbidity

NO IDEAL MATERIAL !!!!





Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr)

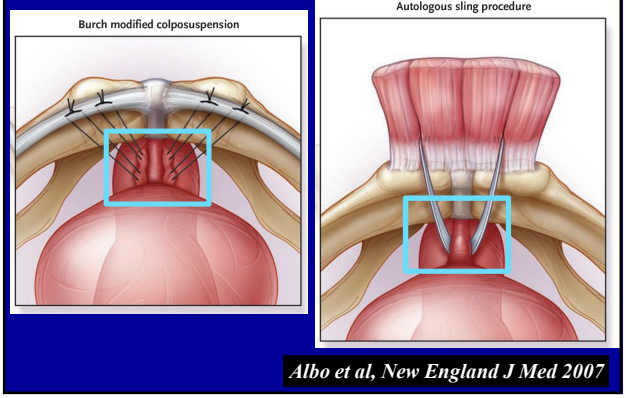
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence

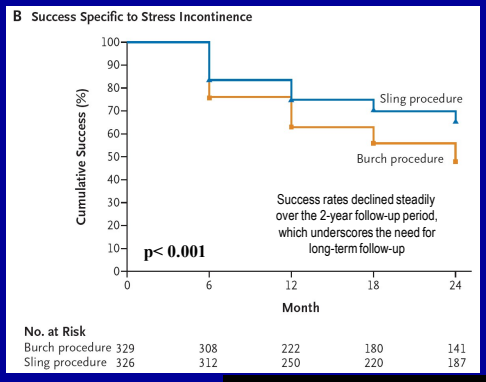
Michael E. Albo, M.D., Holly E. Richter, Ph.D., M.D., Linda Brubaker, M.D., Peggy Norton, M.D., Stephen R. Kraus, M.D., Philippe E. Zimmern, M.D., Toby C. Chai, M.D., Halina Zyczynski, M.D., Ananias C. Diokno, M.D., Sharon Tennstedt, Ph.D., Charles Nager, M.D., L. Keith Lloyd, M.D., MaryPat FitzGerald, M.D., Gary E. Lemack, M.D., Harry W. Johnson, M.D., Wendy Leng, M.D., Veronica Mallett, M.D., Anne M. Stoddard, Sc.D., Shawn Menefee, M.D., R. Edward Varner, M.D., Kimberly Kenton, M.D., Pam Moalli, M.D., Larry Sirls, M.D., Kimberly J. Dandreo, M.Sc., John W. Kusek, Ph.D., Leroy M. Nyberg, M.D., Ph.D., and William Steers, M.D., for the Urinary Incontinence Treatment Network*

SISTEr- surgical procedures



Albo et al, New England J Med 2007

SISTEr - Results



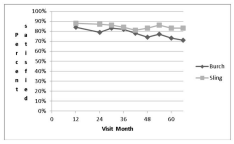
Albo et al, New England J Med 2007

5-y follow-up of the SISTEr trial

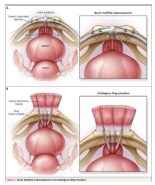
	Burch	fascial sling
5-y continence rate:	24.1%	30.8%
5-y satisfaction rate:	73%	83%
adverse events:	10%	9%

eau Guidelines

Alternatives – Burch and PVS



Brubaker et al. 5-year continence rates, satisfaction and adverse events of burch urethropexy and fascial sling surgery for urinary incontinence. J Urol. 2012 187:1324-30



Albo et al. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med. 2007 ;356:2143-55

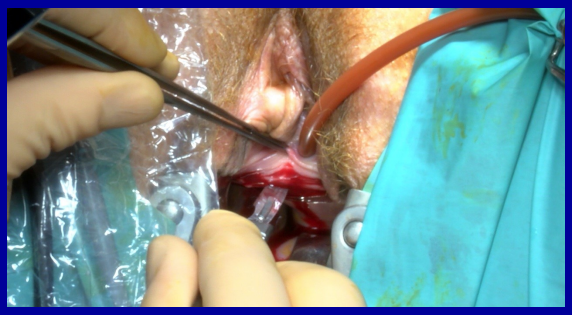
Colposuspension and autologous fascial sling 70-90% satisfaction rates

Novara G et al. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol 2010;58:218–38
Lapitan MCM, Cody JD, Mashayekhi A. Open retropubic colposuspension for urinary incontinence in women. Cochrane Database Syst Rev. 2017 Jul 25;7

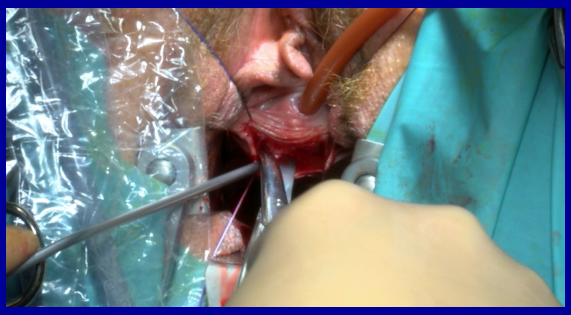
www.uroweb.org/guidelines #eauguidelines

Injecting local and adrenaline

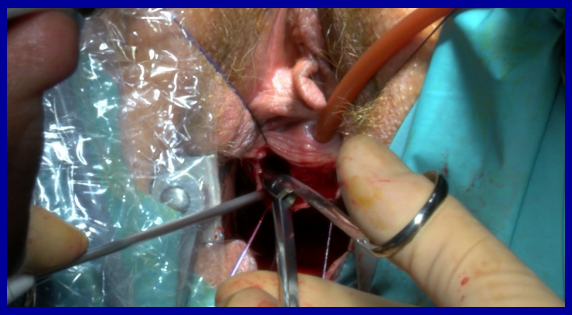
Transverse vagina incision



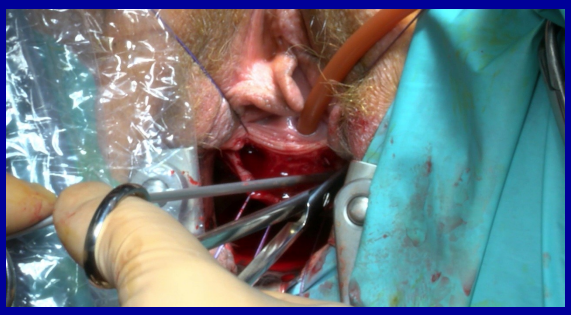
Dissection of vaginal flap



Dissection under the pubic bone either side

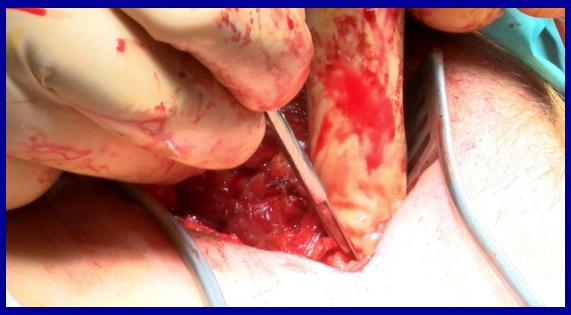


Dissection under the pubic bone either side

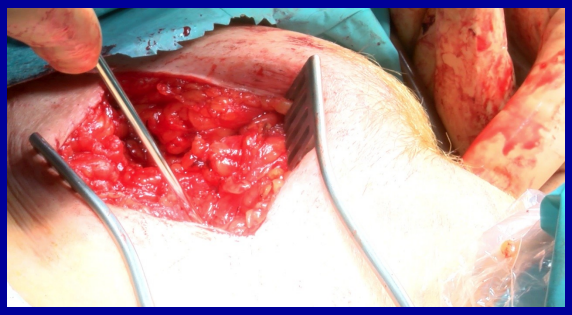


Using looped nylon on double sling thickness to fix sling on either side

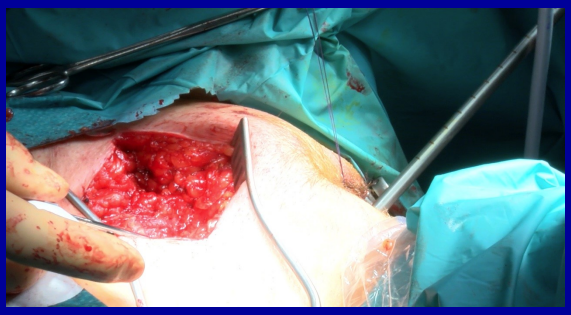
A stab in the rectus sheathe to introduce the needle



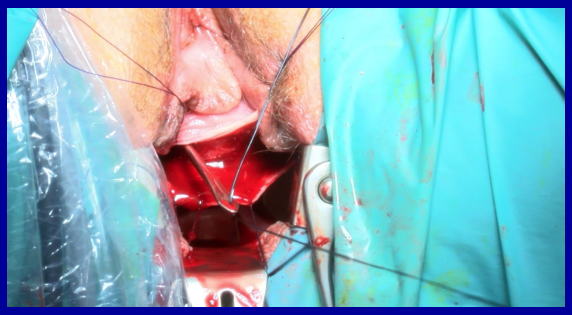
Direct the needle towards a finger in the previous dissection of the vagina



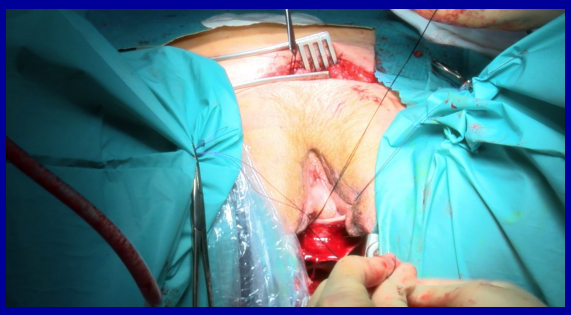
Cystoscopy while the needle is in place to R/O bladder injury before passing the suture



Feeding the suture in the McGuire needle



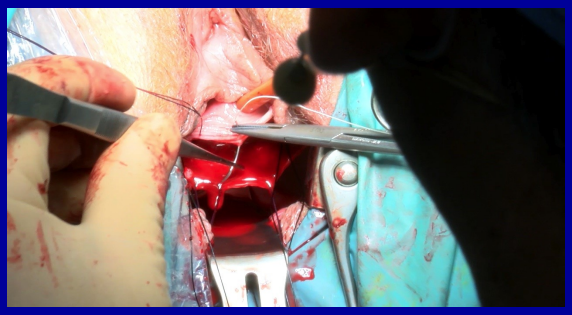
Pulling the suture upward



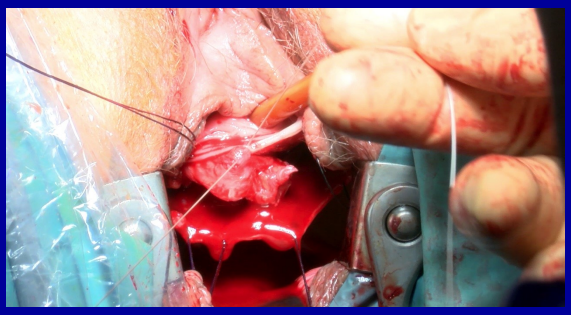
The same is done to the other side

Sling is now in place

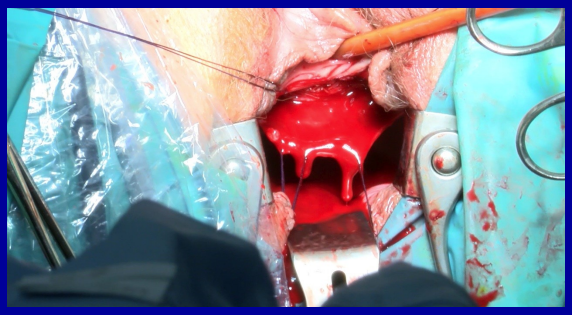
A stich to fix the sling to the vagina in the midline and prevent migration



A stich to fix the sling to the vagina in the midline and prevent migration

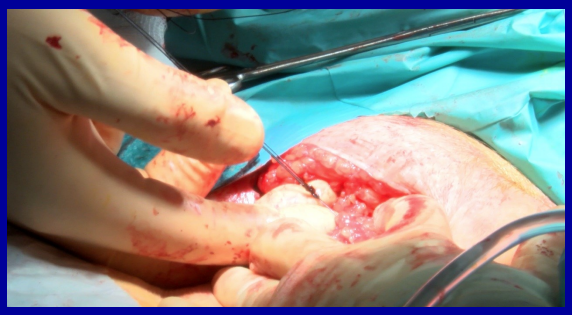


Stiches pulled and sling in place



Tying the stiches loose with two fingers underneath

Tying the stiches loose with two fingers underneath



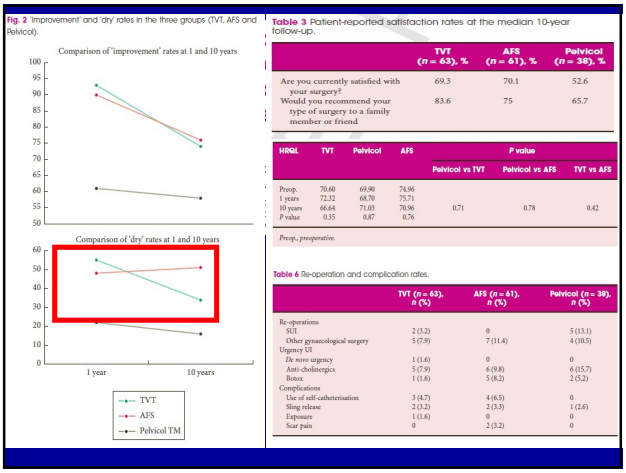


Table 3 Patient-reported satisfaction rates at the median 10-year follow-up.

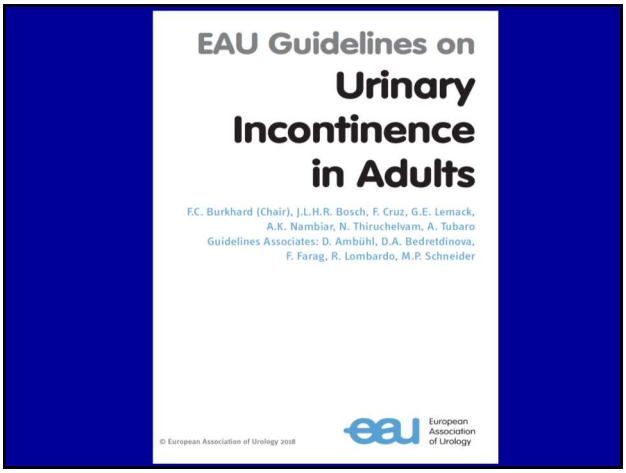
	TVT (*n* = 63), %	AFS (*n* = 61), %	Pelvicol (*n* = 38), %
Are you currently satisfied with your surgery?	69.3	70.1	52.6
Would you recommend your type of surgery to a family member or friend	83.6	75	65.7

HRQL	TVT	Pelvicol	AFS	*P* value		
				Pelvicol vs TVT	Pelvicol vs AFS	TVT vs AFS
Preop.	70.60	69.98	74.96			
1 years	72.32	68.70	75.71			
10 years	66.64	71.03	70.96	0.71	0.78	0.42
P value	0.35	0.87	0.76			

Preop., preoperative.

Table 6 Re-operation and complication rates.

	TVT (*n* = 63), *n* (%)	AFS (*n* = 61), *n* (%)	Pelvicol (*n* = 38), *n* (%)
Re-operations			
SUI	2 (3.2)	0	5 (13.1)
Other gynaecological surgery	5 (7.9)	7 (11.4)	4 (10.5)
Urgency UI			
De novo urgency	1 (1.6)	0	0
Anti-cholinergics	5 (7.9)	6 (9.8)	6 (15.7)
Botox	1 (1.6)	5 (8.2)	2 (5.2)
Complications			
Use of self-catheterisation	3 (4.7)	4 (6.5)	0
Sling release	2 (3.2)	2 (3.3)	1 (2.6)
Exposure	1 (1.6)	0	0
Scar pain	0	2 (3.2)	0



Recommendations	Strength rating
Offer a MUS to women with uncomplicated SUI	Strong
Inform women of the unique complications associated with each individual procedure.	Strong
Inform women who are being offered a single-incision sling that long-term efficacy remains uncertain.	Strong
Inform women undergoing colposuspension that there is a longer duration of surgery, hospital stay and recovery, as well as a high risk of development of pelvic organ prolapse and voiding dysfunction post-operatively.	Strong
Inform older women with SUI about the increased risks associated with surgery, including the lower probability of success.	Weak
Inform women that any vaginal surgery may have an impact on sexual function, which is generally positive.	Weak
Only offer new devices, for which there is no level 1 evidence base, as part of a structured research programme.	Strong
Only offer adjustable MUS as a primary surgical treatment for SUI as part of a structured research programme.	Strong
Offer bulking agents to women with SUI who request a low-risk procedure with the understanding that repeat injections are likely and long-term durability is not established.	Strong

MUS = mid-urethral sling; SUI = stress urinary incontinence.

Summary of evidence	LE
Autologous fascial sling is more effective than colposuspension for improvement of SUI.	1b
Autologous fascial sling has a higher risk of operative complications than open colposuspension, particularly voiding dysfunction and post-operative UTI.	1b
Colposuspension is associated with a higher long-term risk of POP than MUS.	1a
Laparoscopic colposuspension has a shorter hospital stay and may be more cost-effective than open colposuspension.	1a

POP = pelvic organ prolapse; SUI = stress urinary incontinence ; UTI = urinary tract infection.

Recommendations	Strength rating
Management of complicated SUI should only be offered in expert** centres.	Weak
The choice of surgery for recurrent SUI should be based on careful evaluation of the individual patient including multichannel urodynamics and imaging as appropriate.	Weak
Inform women with recurrent SUI that the outcome of a surgical procedure, when used as a second-line treatment, is generally inferior to its use as a first-line treatment, both in terms of reduced efficacy and increased risk of complications.	Weak
Consider secondary synthetic sling, colposuspension or autologous sling as first options for women with complicated SUI.	Weak
Inform women receiving AUS or ACT© that although cure is possible, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	Weak

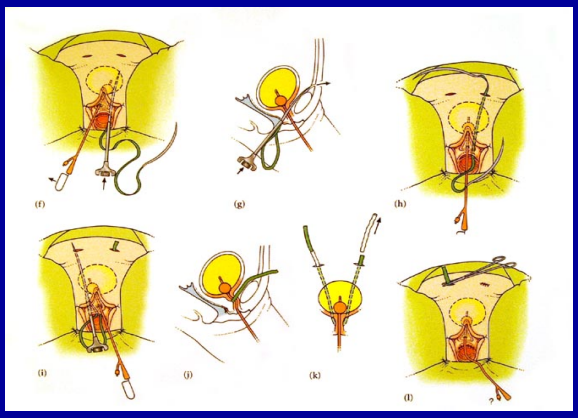
ACT© = Adjustable compression device; AUS = artificial urinary sphincter; SUI = stress urinary incontinence; UI = urinary incontinence.
*** Expert centres refers to the comments on surgeon volume in the introduction to the surgical chapter.*

Recommendations for women requiring surgery for bothersome pelvic organ prolapse who have symptomatic or unmasked SUI	Strength rating
Offer simultaneous surgery for pelvic organ prolapse and SUI.	Strong
Inform women of the increased risk of adverse events with combined surgery compared to prolapse surgery alone.	Strong
Recommendations for women requiring surgery for bothersome pelvic organ prolapse who do not have symptomatic or unmasked SUI	
Inform women that there is a risk of developing *de novo* SUI after prolapse surgery.	Strong
Warn women that the benefit of surgery for SUI may be outweighed by the increased risk of adverse events with combined surgery compared to prolapse surgery alone.	Strong

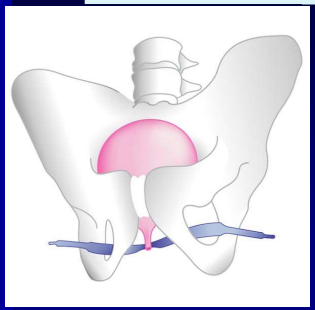
POP = pelvic organ prolapse; SUI = stress urinary incontinence; UI = urinary incontinence.

Conclusions

- Autologous fascial sling on a string is a has good subjective cure rates for primary and recurrent SUI
- Complication rates are acceptable
- It is an easily learned technique and avoids the risk of erosion of artificial MUS



Trans Obturator Tape - TOT



- Tape runs through both obturator foramina
- Cystoscopy not necessary (bladder perforation unlikely)
- No long term follow-up data

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Retropubic versus Transobturator Midurethral Slings for Stress Incontinence

Holly E. Richter, Ph.D., M.D., Michael E. Albo, M.D., Halina M. Zyczynski, M.D., Kimberly Kenton, M.D., Peggy A. Norton, M.D., Larry T. Sirls, M.D., Stephen R. Kraus, M.D., Toby C. Chai, M.D., Gary E. Lemack, M.D., Kimberly J. Dandreo, M.Sc., R. Edward Varner, M.D., Shawn Menefee, M.D., Chiara Ghetti, M.D., Linda Brubaker, M.D., Ingrid Nygaard, M.D., Salil Khandwala, M.D., Thomas A. Rozanski, M.D., Harry Johnson, M.D., Joseph Schaffer, M.D., Anne M. Stoddard, Sc.D., Robert L. Holley, M.D., Charles W. Nager, M.D., Pamela Moalli, M.D., Ph.D., Elizabeth Mueller, M.D., Amy M. Arisco, M.D., Marlene Corton, M.D., Sharon Tennstedt, Ph.D., T. Debuene Chang, M.D., E. Ann Gormley, M.D., and Heather J. Litman, Ph.D., for the Urinary Incontinence Treatment Network*

N ENGL J MED 362;22 NEJM.ORG JUNE 3, 2010

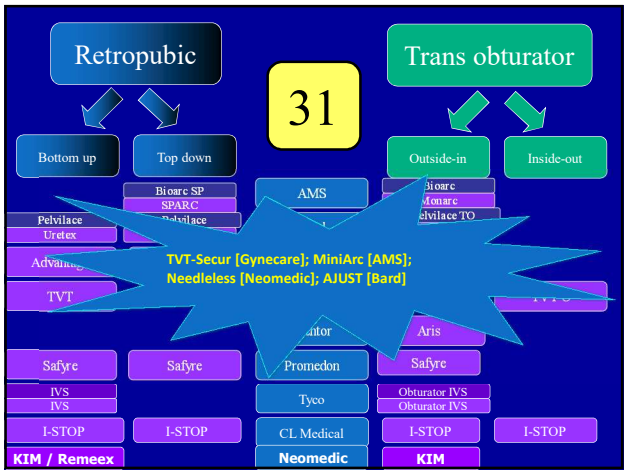
TOMUS Study

5-Year Longitudinal Followup after Retropubic and Transobturator Mid Urethral Slings

Kimberly Kenton,*,† Anne M. Stoddard,‡ Halina Zyczynski,§ Michael Albo,§ Leslie Rickey,‖ Peggy Norton,§ Clifford Wai,§ Stephen R. Kraus,¶ Larry T. Sirls,** John W. Kusek,§ Heather J. Litman,§ Robert P. Chang†† and Holly E. Richter‡‡

From Northwestern University, Chicago, Illinois (KK), New England Research Institutes, Watertown (AMS, RPC), and Boston Children's Hospital, Boston (HJL), Massachusetts; University of Pittsburgh, Magee-Women's Research Institute, Pittsburgh, Pennsylvania (HZ); University of California San Diego, San Diego, California (MA); Yale University, New Haven, Connecticut (LR); University of Utah, Salt Lake City, Utah (PN);University of Texas Southwestern, Dallas (CW), and University of Texas Health Sciences Center at San Antonio, San Antonio (SRK), Texas; William Beaumont Hospital, Royal Oak, Michigan (LTS); National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland (JWK); and University of Alabama at Birmingham, Birmingham, Alabama (HER) for the Urinary Incontinence Treatment Network

- Follow-up cohort from TOMUS study
- Success (no re-treatment and no self-reported UI on MESA questionnaire):
  51.3% RPR vs 43.4% TOT
- 404 women; 22 ineligible because of surgical retreatment for SUI (3%)
- 52 non-serious and 6 serious adverse events
- 2 mesh erosions and 6 exposures in both groups combined
- Most common adverse event was UTI



EUROPEAN UROLOGY 58 (2010) 218–238

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Female Urology – Incontinence

Editorial by Firouz Daneshgari on pp. 239–241 of this issue

Updated Systematic Review and Meta-Analysis of the Comparative Data on Colposuspensions, Pubovaginal Slings, and Midurethral Tapes in the Surgical Treatment of Female Stress Urinary Incontinence

Giacomo Novara [a,], Walter Artibani [b], Matthew D. Barber [c], Christopher R. Chapple [d], Elisabetta Costantini [e], Vincenzo Ficarra [a], Paul Hilton [f], Carl G. Nilsson [g], David Waltregny [h]*

[a] *Department of Oncological and Surgical Sciences, Urology Clinic, University of Padua, Padua, Italy*
[b] *Department of Biomedical and Surgical Sciences, Urology Clinic, University of Verona, Verona, Italy*
[c] *Obstetrics, Gynecology, and Women's Health Institute, Cleveland Clinic, Cleveland, Ohio, USA*
[d] *Sheffield Teaching Hospitals NHS Foundation Trust, Department of Urology, The Royal Hallamshire Hospital, Sheffield, UK*
[e] *Section of Urology and Andrology, Department of Medical-Surgical Specialties and Public Health, University of Perugia, Perugia, Italy*
[f] *Directorate of Women's Services, Royal Victoria Infirmary, Newcastle upon Tyne, UK*
[g] *Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland*
[h] *Department of Urology, University of Liège, Liège, Belgium*

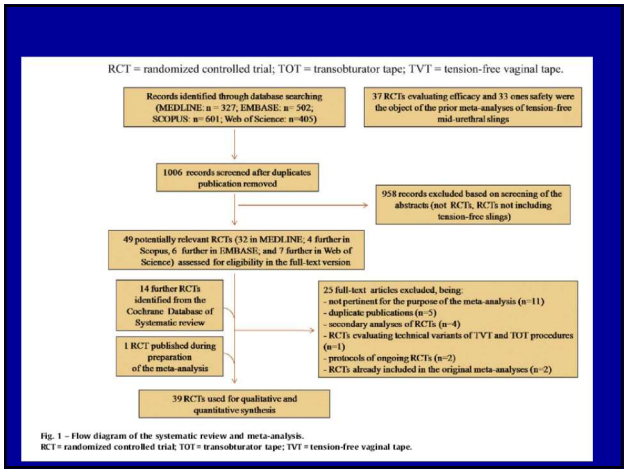
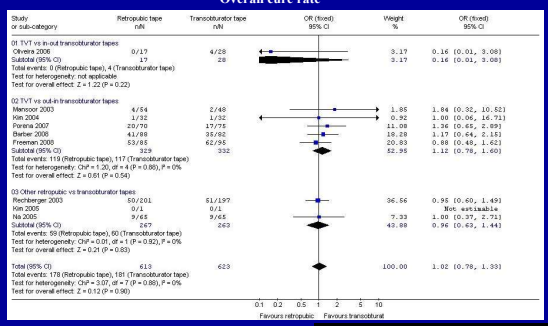


Fig. 1 – Flow diagram of the systematic review and meta-analysis.
RCT = randomized controlled trial; TOT = transobturator tape; TVT = tension-free vaginal tape.

RCTs comparing retropubic to trans-obturator tension-free midurethral tapes

Overall cure rate



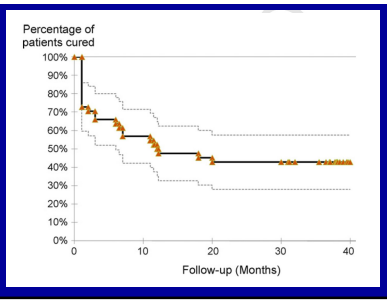
Novara G, et al. Eur Urol 2010; 58: 218-38

EUROPEAN UROLOGY 58 (2010) 157–161

Female Urology – Incontinence

Midterm Prospective Evaluation of TVT-Secur Reveals High Failure Rate

Jean-Nicolas Cornu, Philippe Sèbe, Laurence Peyrat, Calin Ciofu, Olivier Cussenot, Francois Haab*



•Format: Abstract

Send to

Eur Urol. 2014 Feb;65(2):402-27. doi: 10.1016/j.eururo.2013.08.032. Epub 2013 Aug 29.

Single-incision mini-slings versus standard midurethral slings in surgical management of female stress urinary incontinence: an updated systematic review and meta-analysis of effectiveness and complications.

Mostafa A[1], Lim CP[2], Hopper L[1], Madhuvrata P[3], Abdel-Fattah M[4].

Author information

CONTEXT:

An updated systematic review and meta-analysis of randomised controlled trials (RCTs) comparing single-incision mini-slings (SIMS) versus standard midurethral slings (SMUS) in the surgical management of female stress urinary incontinence (SUI).

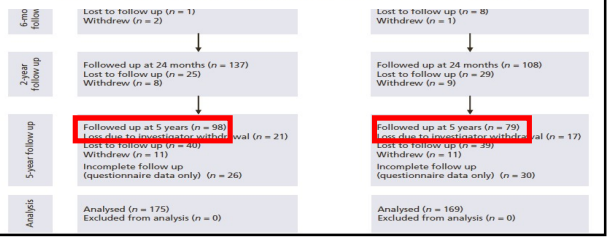
- SIMS were associated with earlier recovery and earlier return to normal activities and to work.
- One RCT showed substantive cost savings for health provider in the SIMS arm.
- Results should be interpreted with caution due to the trends towards better clinical outcomes with SMUS/ heterogeneity of the trials included/ relatively short FU.

Robert Jones
Paul Abrams
Paul Hilton
Karen Ward
Marcus Drake*
*Southmead Hospital, Bristol
Avon, United Kingdom*

Neurourology and Urodynamics 29:40–41 (2010)

LETTER TO THE EDITOR

Risk of Tape-Related Complications After TVT Is At Least 4%



eau Guidelines

FDA notifications

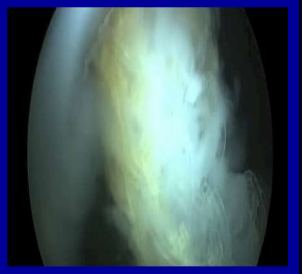
- **2008**: complications associated with mesh us for SUI and POP were "rare."
- **2011**: complications from mesh used to treat POP were "not rare".

(This report did not comment on safety of mesh for SUI)

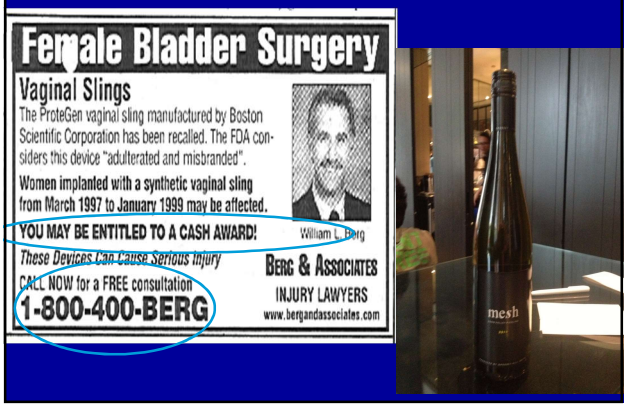
- **2012**: report on the safety of slings for SUI - concluded that the safety of multi-incision slings is supported by the evidence for up to 1 year.
- **2016**: 2 final orders.

- Reclassified mesh for the treatment of POP from Class II (moderate-risk devices) to Class III (high-risk devices).
- Manufacturers required to submit premarket approval applications for transvaginal mesh used in the treatment of POP.

Mesh erosion ~ 9%

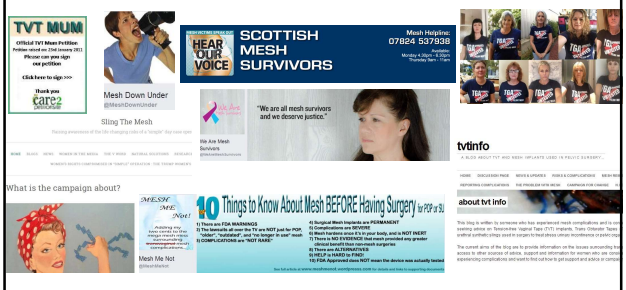


Beware

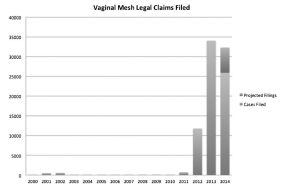


If no concerns, why so many support groups?

eau Guidelines

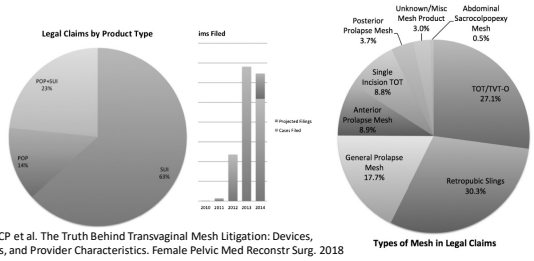


If no concerns, why so many lawsuits?



Souders CP et al. The Truth Behind Transvaginal Mesh Litigation: Devices, Timelines, and Provider Characteristics. Female Pelvic Med Reconstr Surg. 2018 24:21-25

If no concerns, why so many lawsuits?



Souders CP et al. The Truth Behind Transvaginal Mesh Litigation: Devices, Timelines, and Provider Characteristics. Female Pelvic Med Reconstr Surg. 2018 24:21-25

Mesh Erosion

- UK HES Data, 92,246 patients underwent SUI mesh insertion
- 5.9 % readmitted for a further mesh intervention or for symptoms of mesh complications within 5 years of their first-time mesh procedure
- Multiple readmissions

Total number of patients in cohort (total duration of follow-up)	TVT		TOT	
	41,880 (175,284 patient years)		25,509 (108,339 patient years)	
	Total	Patients	Total	Patients
In-hospital deaths	–	345 (0.8%)	–	204 (0.8%)
Readmissions for further surgery	2476	2016 (4.8%)	1370	1161 (4.6%)
- *removal*	*1277*	*1112 (2.7%)*	*541*	486 (1.9%)
- *repair*	*459*	*435 (1.0%)*	*240*	227 (0.9%)
- *insertion*	*831*	*812 (1.9%)*	*630*	615 (2.4%)
- *renewal*	*5*	*5 (0.0%)*	*1*	1 (0.0%)
Readmissions for complications from mesh surgery	1389	1047 (2.5%)	607	484 (1.9%)
Readmissions for complications *or* further surgery	2950	2248 (5.4%)	1580	1255 (4.9%)
Readmissions/1000 person years:				
- further mesh surgery	14.1	–	12.7	–
- complications of mesh surgery	7.9	–	5.6	–
- complications *or* further surgery	16.8	–	14.6	–
Patients free from further surgery or admission for complications after 5 years [95% CI] %	–	93.9 [93.7–94.2]	–	94.4 [94.1–94.8]

Procedure type	Number of readmissions				Maximum number of readmissions
	0	1	2	3+	
TVT	39,632 (94.6)	1737 (4.1)	375 (0.9)	136 (0.3)	6
TOT	24,254 (95.1)	1017 (4.0)	174 (0.7)	64 (0.3)	6

Keltie et al. Complications following vaginal mesh procedures for stress urinary incontinence: an 8 year study of 92,246 women. Sci Rep 2017 7:12

Erosion

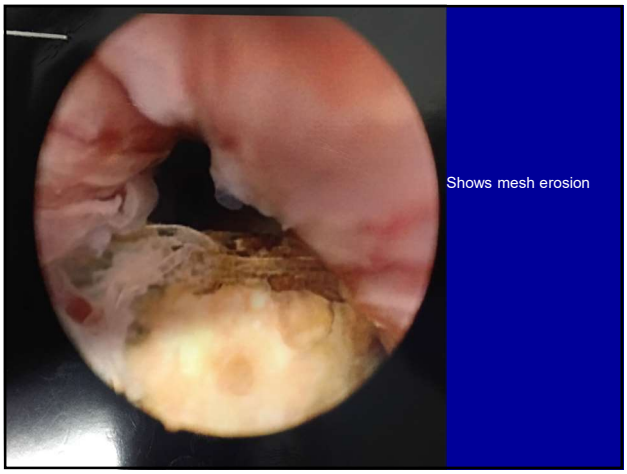
- 2.4% mesh erosions
  - (MHRA York report 2012)
- 2.09% mesh erosions

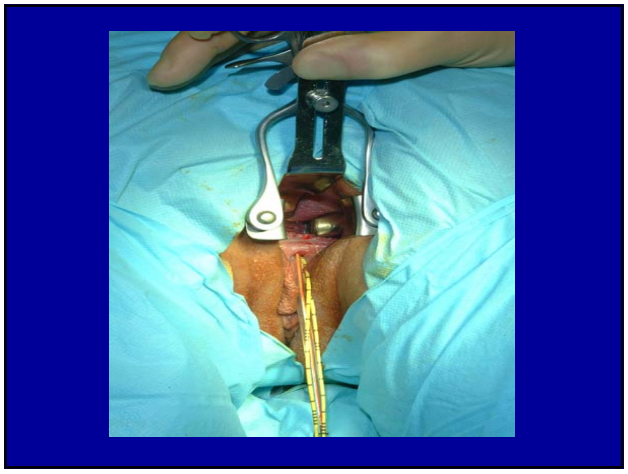
(Ford AA et al Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev 2017)

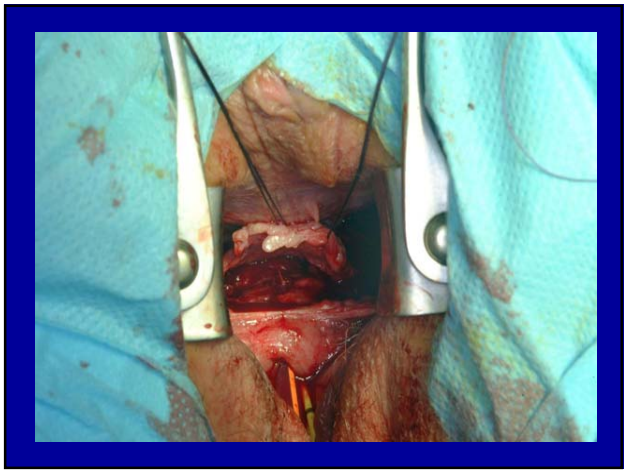
Tape erosion

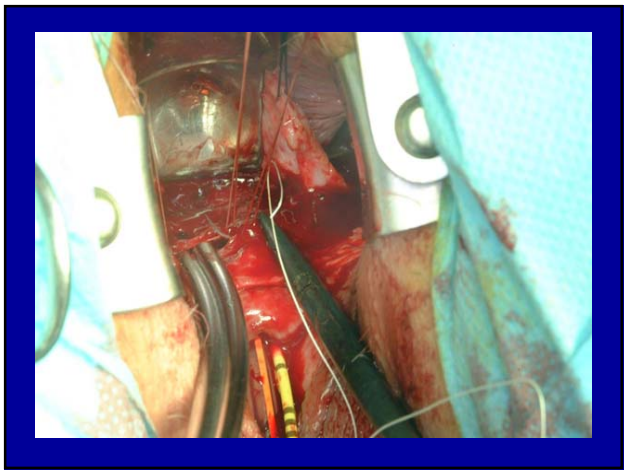
Mrs JF aged 50

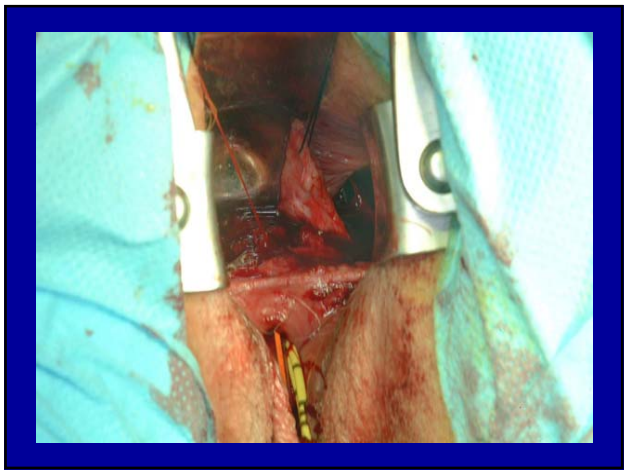
- History of stress incontinence
- 2005 TOT (transobturator tape)
- 2006 TOT for persistent SUI
- 2006 TVT (transvaginal tape)for persistent SUI
- Post-op was dry but had voiding dysfunction and had to do self catheterisation for 3 months

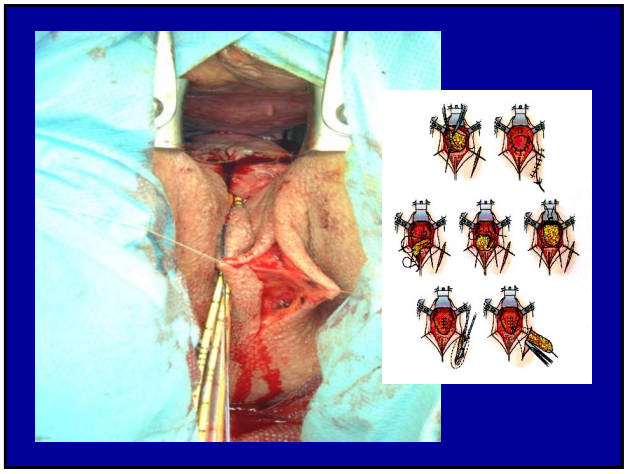

Shows mesh erosion

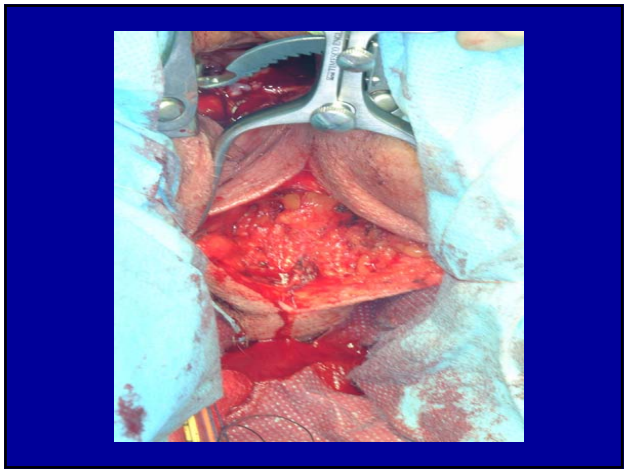


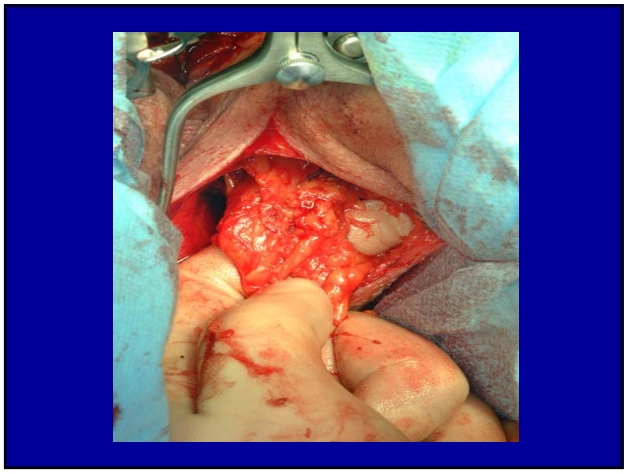


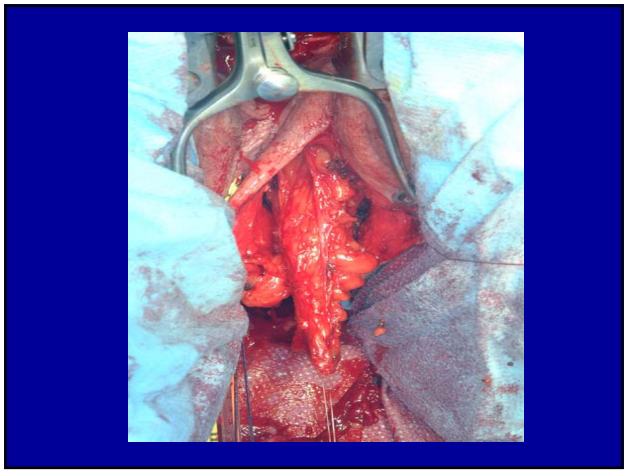


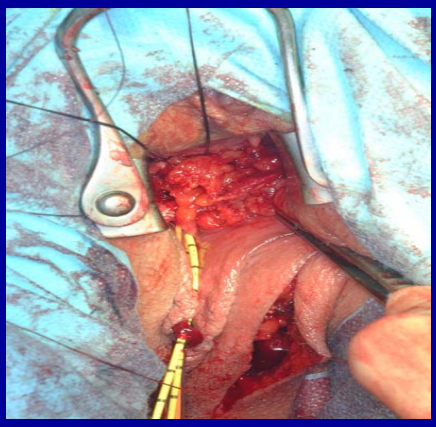


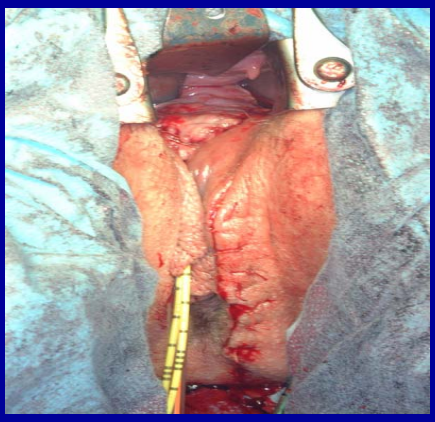












Post-operative Management

- Remove vaginal pack & Martius donor site drain at 24 hours
- Suprapubic catheter
- Leave urethral catheter for 2-3 weeks
- Oral antibiotics until catheter removed

Sexual dysfunction

- 9.3% painful intercourse and *de novo* or worsening coital incontinence
- (MHRA York report 2012)
- 9.4% sexual dysfunction

- (Jha et al. Impact of incontinence surgery on sexual function: a systematic review and meta-analysis. J Sex Med. 2012 9:34-43)

Voiding dysfunction and Urgency

- 5.53% voiding dysfunction
- 8.35% de novo urgency and UUI

Voiding dysfunction (short and medium term, up to 5 years)	Study population		RR 0.53 (0.43 to 0.65)	6217 (37 RCTs)	⊕⊕⊕◯ MODERATE [6]
	72 per 1000	38 per 1000 (31 to 47)			
	Mean control group risk across studies				
	55 per 1000	29 per 1000 (24 to 36)			
De novo urgency or urgency incontinence (short term, up to 12 months)	Study population		RR 0.98 (0.82 to 1.17)	4923 (31 RCTs)	⊕⊕⊕◯ MODERATE [7]
	82 per 1000	80 per 1000 (67 to 96)			
	Mean control group risk across studies				
	83 per 1000	81 per 1000 (68 to 97)			

(Ford AA et al Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev 2017)

Conservative Treatment Options

- Watchful waiting
- Intermittent catheterization
- Indwelling catheter
- Pharmacotherapy to control associated overactivity
- Dilation (??) – I do not recomend

Definitive Treatment Options

Midurethral Synthetic Sling

- Sling incision
- Sling loosening (early)
- Urethrolysis

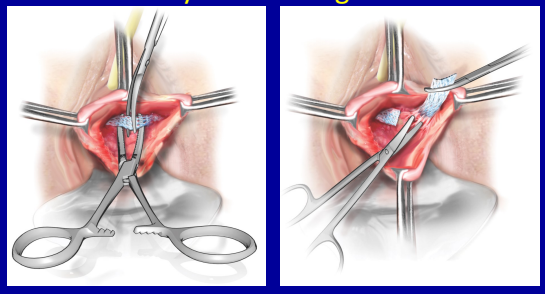
Traditional Slings

- Sling Incision (PV sling)
- Urethrolysis
  - Transvaginal
  - Retropubic
  - Suprameatal (infrapubic)
- Cut suspension/sling sutures
  - *No published peer-reviewed*

Technique of Mid Urethral Sling Loosening 1-2 weeks

- Infiltrate anterior vaginal wall with 1% lidocaine
- Open vaginal suture line
- The sling is identified and hooked with a right-angle clamp
- Spreading of the right angle clamp or downward traction on the tape will usually loosen it (1-2 cm)
- If the tape is fixed, it can be cut
- Reapproximate vaginal wall

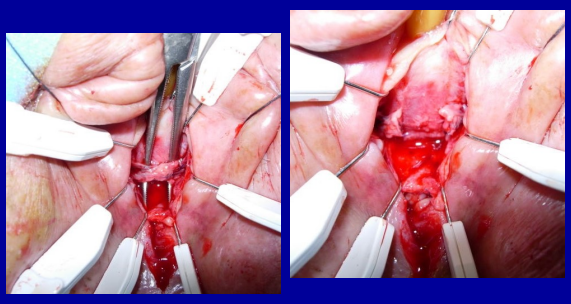
Midurethral Synthetic Sling Incision



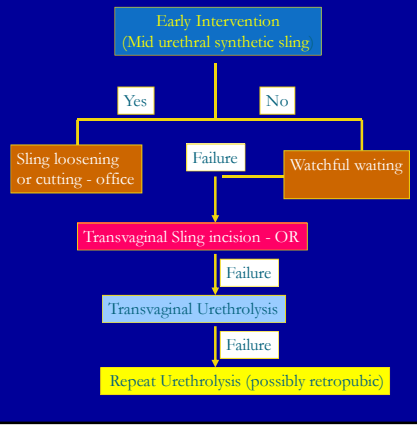
- If the sling is difficult to identify, can go lateral to the midline especially for TO slin
- It is critical to identify the sling with certainty (consider pathologic confirmation)

Illustrations from Vaginal Surgery for The Urologist
Nitti VW. Rosenblum NBrucker BM Elseiver. 2012

Obstructing Midurethral Sling at 11 months



Obstructing Sling Algorithm



Summary

- Clinically significant obstruction after sling surgery incontinence surgery may not be "common" but occurs even in the most experienced hands
- Sling incision and urethrolysis, by a variety of techniques, are successful in restoring emptying and relieving LUTS in a majority of cases
  - Some studies "suggest early rather than late is better
- The diagnosis is most often made based on

EUROPEAN UROLOGY 64 (2013) 525–529

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion – Collaborative Editorial

Mesh Sling in an Era of Uncertainty: Lessons Learned and the Way Forward

Christopher R. Chapple[a], Shlomo Raz[b], Linda Brubaker[c], Philippe E. Zimmern[d,*]

[a]Department of Urology, Royal Hallamshire Hospital, Sheffield, UK; [b]Frank Gehr Urological Center, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA; [c]Stritch School of Medicine, Loyola University Chicago, IL, USA; [d]UT Southwestern Medical Center, Dallas, TX, USA

- New surgical devices should be adequately assessed before introduction into clinical practice.

PROPER ASSESSMENT OF NEW DEVICES

- Surgeons should carry out surgery for SUI only if they are adequately trained in the subspecialty and after appropriate evaluation of the patient.
- Although mesh insertion seems like an easy procedure, treating complications of mesh surgery may require extensive and complex procedures.

PROPER TRAINING

- Surgeons are not properly informing patients regarding their personal experience, number of cases done, and potential complications.
- Patients are not well informed. Patients should have more access to information about the potential complications of mesh.

PATIENT INFORMATION

- Complications are underreported. The reporting system for patients, physicians, and manufacturers should be improved.
- *Even with complete mesh removal, >30% of patients may be permanently disabled or may experience long-term symptoms.*

COMPLICATIONS REPORTING

EAU Mesh Consensus Meeting
Amsterdam
20 November 2016

EUROPEAN UROLOGY 72 (2017) 424–431

available at www.sciencedirect.com
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European Association of Urology

Review – Incontinence

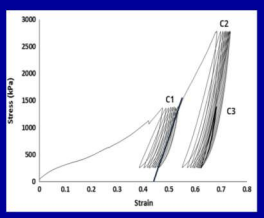
Consensus Statement of the European Urology Association and the European Urogynaecological Association on the Use of Implanted Materials for Treating Pelvic Organ Prolapse and Stress Urinary Incontinence

Christopher R. Chapple[a,], Francisco Cruz[b,c], Xavier Deffieux[d], Alfredo L. Milani[e], Salvador Arlandis[f], Walter Artibani[g], Ricarda M. Bauer[h], Fiona Burkhard[i], Linda Cardozo[j], David Castro-Diaz[k], Jean Nicolas Cornu[l], Jan Deprest[m], Alfons Gunnemann[n], Maria Gyhagen[o], John Heesakkers[p], Heinz Koelbl[q], Sheila MacNeil[r], Gert Naumann[s], Jan-Paul W.R. Roovers[t], Stefano Salvatore[u], Karl-Dietrich Sievert[v], Tufan Tarcan[w], Frank Van der Aa[x], Francesco Montorsi[y], Manfred Wirth[z], Mohamed Abdel-Fattah[aa]*

Patient summary: Synthetic slings can be safely used in the surgical treatment of stress incontinence in both male and female patients. Patients need to be aware of the alternative therapy and potential risks and complications of this therapy. Synthetic mesh for treating prolapse should be used only in complex cases with recurrent prolapse in specialist referral centres.

Evidence that PP mesh is not fit for purpose in the pelvic floor

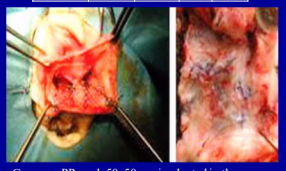
In vitro failure of PP mesh



Cyclic tests: stress-strain curves for Prolene mesh, straight line was fitted to the 10th loading curve at each force level for calculation of stiffness. Rightward shifts of the hysteresis loops indicate permanent elongation of the mesh, or possibly long-term viscous creep. (Mech Behav Biomed Mater. 2014 37:48-55, Li et al).

In vivo PP mesh failure in sheep

Implantation	Contraction (%)		Exposure	
	60 days	90 days	60 days	90 days
Abdominal	9.35±4.56 (n=10)	7.9±10.1 (n=9±1)	0	0
Vaginal	51.0±11.2 (n=7)	55.0±7.0 (n=5)	2/5 (n=5)	1/5 (n=5)



Gynecare PP mesh 50x50mm implanted in the abdomen or vagina of sheep. Results indicate both contraction and exposure are site specific for the PP mesh. Mesh in vagina exposed in 3/10 sheep by 90 days (BJOG 2013 120, 2: 244–250 Manodoro et al).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Overactive bladder: concept & practical management

Paulo Palma
Professor Titular de Urologia
UNICAMP
CAU Academy member

Overactive Bladder Syndrome

'Urgency with or without urge incontinence, usually with frequency and nocturia'

Abrams et al, 2002

Symptom complex, not a urodynamic diagnosis

ICS

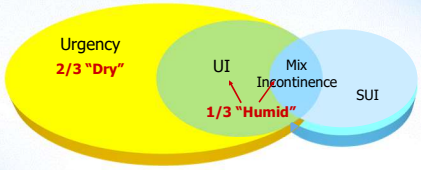
Detrusor Overactivity

A urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked.

Abrams et al, 2002

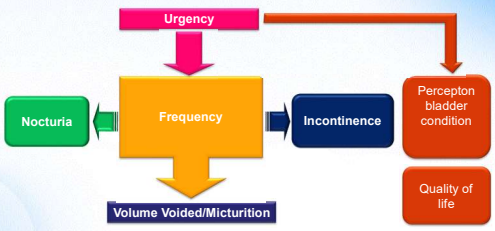
ICS

OAB & urinary incontinence



Heron Report 2003
Milsom I et al., BJU Int 2001; 87:760-6
Stewart WF et al., World J Urol 2003; 20: 327-336

Urgency is the primary symptom



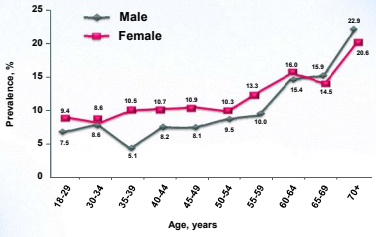
Modified from Chapple CR , Artibani W, Cardozo LD, Castro-Diaz D, Craggs M, Haab F et al. BJU Int. 2005; 95: 335–40

Measuring urgency

- The Urgency Perception Scale (UPS)
  - Describes the ability of a patient to hold urine and finish tasks before going to the toilet

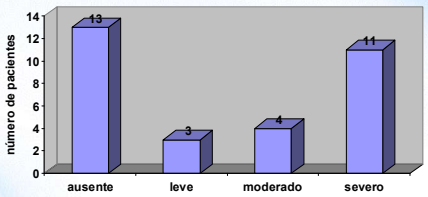
Cardozo L et al BJU Int 2005; 95:591-596

Gender prevalece



Irwin DE, Milsom I, Hunskaar S et al *Eur Urol* 2006; 50: 1306-15

Impact on sexuality



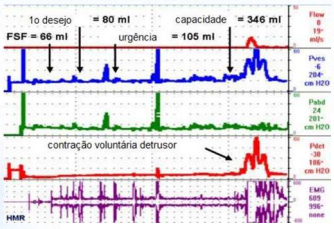
Palma P, Thiel R, Urod & urogin, 2003

Management options

- Urodynamics
- Syndrome
- Fenotypes

Urodynamic classification (Blaivas)

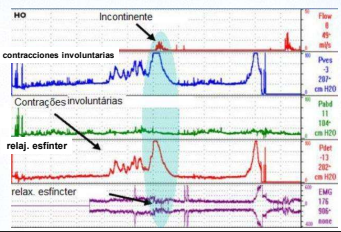
- Type 1: OAB symptoms, no involuntary contractions



Urodynamic classification (Blaivas)

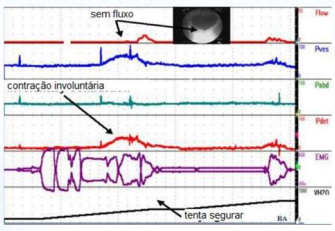
Type 2 : involuntary contractions, patient can interrupt

incontinente



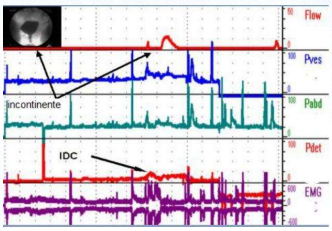
Urodynamic classification (Blaivas)

- Type 3 : Temporally continente contracting the sphincter



Urodynamic classification (Blaivas)

Type 4: No sphincter control



EUROPEAN UROLOGY 75 (2019) 988–1000
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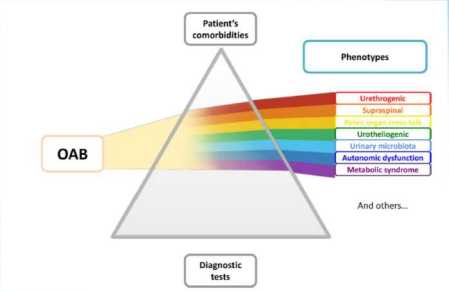
European Association of Urology

Review – Female Urology – Incontinence – Editor's Choice

A Comprehensive Review of Overactive Bladder Pathophysiology: On the Way to Tailored Treatment

Benoit Peyronnet [a,], Emma Mironska [b], Christopher Chapple [b], Linda Cardozo [c], Matthias Oelke [d], Roger Dmochowski [e], Gérard Amarenco [f], Xavier Gamé [g], Roger Kirby [h], Frank Van Der Aa [i], Jean-Nicolas Cormi [j]*

Comorbidities



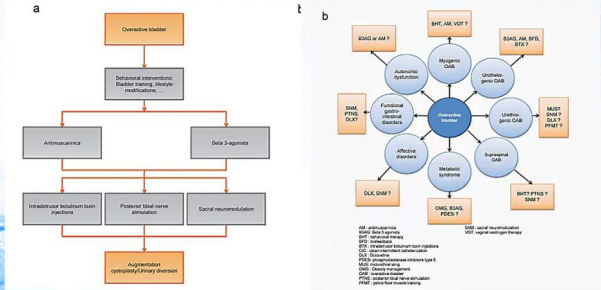
OAB phenotypes- comorbidities

Table 1 – Possible OAB phenotypes

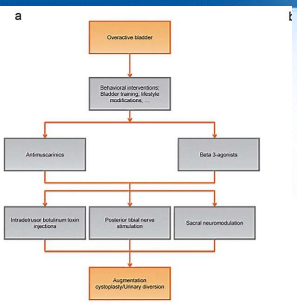
Phenotyping according to pathophysiological factors	Phenotyping according to urodynamic demonstration of detrusor overactivity
Metabolic syndrome	Myogenic
Affective disorders	Urotheliogenic
Sex hormone deficiency	Urethrogenic
Urinary microbiota	Supraspinal
Functional gastrointestinal disorders	Urotheliomyogenic: detrusor underactivity
Autonomic nervous system dysfunction	

OAB = overactive bladder.

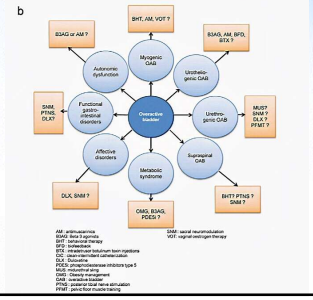
OAB



OAB



Tailored approach to comorbidities



OAB syndrome

- **Less expensive**
- **Empiric, less effective**
- **No identification of the cause**
- **Impossible to understand differece between patients**

Phenotypes

- **More expenesive**
- **Better treatment results**
- **Treatment of comorbidities**

Non-invasive Treatments

- Lifestyle intervention
- Behavioural intervention
- Electrical stimulation
- Acupuncture
- Hypnotherapy
- Drugs

Lifestyle Intervention: fluid Intake

- Many DO sufferers restrict fluid intake even before presentation
- No epidemiological relationship between total fluid intake and urge incontinence

  Wyman et al, 1991
- Excessive fluid intake increases frequency and urgency
- Risk of UTI and worsening constipation with fluid restriction

Lifestyle Intervention: caffeine

- High caffeine intake is an independent risk factor for detrusor overactivity

  Arya, Myers et al, 2000
- Tea drinking (but not coffee) epidemiologically associated with all forms of incontinence

  Hannested et al, 2003 (EPINCONT)
- Caffeine intake pre-urodynamics associated with an increase in cystometric filling pressures

  Creighton, Stanton et al, 1990

International Consultation on Incontinence
Weight Reduction

- Obesity is an independent risk factor for urinary incontinence
- Level 2 evidence that weight loss decreases incontinence in morbidly obese women
- Some level 1 evidence that weight loss also effective for moderately obese women

Weight Reduction

- 5-10% weight loss effective for both stress incontinence and OAB for women with moderate obesity

  Subak, Johnson et al, 2002
- Significant improvements both in pad weights and KHQ scores with 10% weight loss

  Auwad, Bombieri and Freeman, 2005

Behavioural Intervention

- Improves central control
- Underlying psychological abnormality
- Learn / re-learn both conscious and unconscious physiological processes
- Avoids side effects of drugs

Bladder Retraining

- Bladder discipline

  Jeffcoate & Francis, 1966; Frewen, 1978
- Bladder drill

  Jarvis & Miller, 1980
- Inpatient bladder drill improves voiding interval, IEF and nocturia

  Majumar, Tooz-Hobson et al, 2005

International Consultation on Incontinence
Bladder training

- Level 1 evidence that bladder training is more effective than no treatment
- Should be considered as first line treatment for detrusor overactivity

Biofeedback

- Makes subjects aware of normally unconscious physiological processes
- Subjective or objective cure in 81%

  Cardozo et al, 1978
- High relapse rate at 5 years

  Cardozo et al, 1984
- Time consuming, and requires strong motivation

Acupuncture

- Many uncontrolled trials showing subjective benefit
- Single RCT using "placebo acupuncture"
- 85 women randomised

Emmons and Otto, 2005

Acupuncture

- 59% decrease in IEF (40% placebo, p>0.05)
- 14% reduction in frequency (p=0.013)
- 13% increase in volume per void (p=0.01)
- 54% decrease in UDI and IIQ (30% placebo, p<0.001)

Emmons and Otto, 2005

Electrical Stimulation

- Restores inhibitory reflexes via pudendal afferents
- Stimulates inhibitory pathway of micturition centre
- 80% improved or cured

Fall & Maderbacher, 1994

Pelvic floor exercises for DO

- Many RCTs assess pelvic floor exercises in stress incontinence
- No RCTs specifically address urge incontinence
- Improvements seen in most trials for subgroups of women with mixed incontinence
- No evidence of harm
- The 3rd International Consultation on Incontinence concluded that pelvic floor exercises should be offered as a first line therapy in all patients with mixed or urge incontinence

Conservative Therapy
Conclusions

- Bladder retraining should be considered in all patients with DO
- Weight loss may be effective in overweight and obese women
- Pelvic floor exercises are probably of benefit, at least for mixed incontinence
- Other therapies have high relapse rates, and may have a significant placebo component

Pharmacological treatment

- Antimuscarinics (anti cholinergics)
- β-adrenoceptor agonists
- Botulinum toxin A
- Phosphodiesterase inhibitors
- Anti depressive agents
- Vasopressine analogs
- α-adrenoceptor antagonists
- Prostaglandine synthesis inhibitors/ receptor antagonists
- Vanilloid receptor antagonists
- Estrogens
- Membrane channel modulators

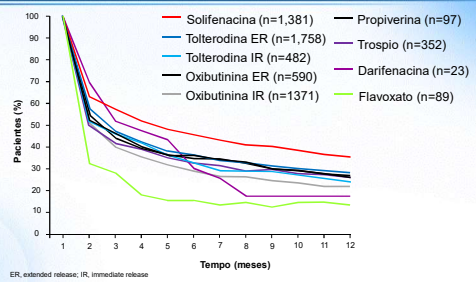
ICI Recoedatios

Antimuscarinics:	Level	Grade
Tolterodine	1	A
Trospium	1	A
Darifenacin	1	A
Solifenacin	1	A
Propantheline	2	B
Atropine, hyoscyamine	3	C

Antimuscarinics

	Droga	Afinidade Receptor	Doses Disponíveis
Sin seletividad M3	Oxibutinina IR	M1, M3	5 mg
	ER		10 mg
	Tolterodina IR	M1, M2, M3, M4, M5	2 mg
	ER		4 mg
	Fesoterodina	M1, M2, M3, M4, M5	4 e 8 mg
	Tróspio	M1, M2, M3,	20 mg
	Propiverina	M1, M2, M3, M4, M5	15 mg
Com seletividad M3	Solifenacina	M3	5 e 10 mg
	Darifenacina	M3	7.5 e 15 mg

Antimuscarinics



ER, extended release; IR, immediate release

Adaptado de Wagg et al. *BJU Int* 2012;110(11):1767-74.

How effective are the antimuscarinics?

What about the patients - do OAB concept and treatments work for them?

- Antimuscarinics are the first-line drug treatment for OAB
  - However, benefits are small
- Median symptom changes with antimuscarinics in RCTs

Urgency:	- 0.9 episodes/24 hours
Urgency incontinence:	- 0.5 episodes/24hours
Frequency:	- 0.8 episodes/24 hours
Nocturia:	- 0.1 episodes/night, NS

Buser et al. *Eur Urol* 2012 (in press) e-published Sept 7, 2012

Received: 22 May 2017 | Accepted: 21 August 2017
DOI: 10.1002/nau.23413

ORIGINAL BASIC SCIENCE ARTICLE

WILEY

Comparative efficacy and tolerability of solifenacin 5 mg/day versus other oral antimuscarinic agents in overactive bladder: A systematic literature review and network meta-analysis

Jameel Nazir PhD[1] | Con Kelleher MD, FRCOG[2] | Samuel Aballéa PhD[3] | Khaled Maman MSc[4] | Zalmai Hakimi PharmD[5] | Colette Mankowski PhD[1] | Isaac Odeyemi PhD[1]

5 | CONCLUSIONS

Identifying the optimum antimuscarinic agent is a key step in the effective management of patients with OAB. This NMA suggests that solifenacin 5 mg/day is more effective than tolterodine 4 mg/day in reducing OAB incontinence and UUI episodes, but does not differ significantly in terms of efficacy compared with other oral antimuscarinics. Solifenacin 5 mg/day has a lower risk of dry mouth compared with approximately half of the antimuscarinic agents assessed. Relative to a selection of other oral antimuscarinics, solifenacin 5 mg/day appears to offer a good balance of efficacy and tolerability, endorsing it as a key pharmacotherapeutic option for the treatment of adults with OAB.

Coll Antropol. 2012 Dec;36(4):1347-53.

Comparison of two selective muscarinic receptor antagonists (solifenacin and darifenacin) in women with overactive bladder--the SOLIDAR study.

But I1, Goldstajn MS, Oreskovic S.

Overactive bladder (OAB) is a common, often debilitating, condition defined as urgency and urge incontinence, usually with frequency and nocturia. The use of muscarinic receptor antagonists are the mainstay of treatment, but their non-selectivity can result in unacceptable adverse effects that limit their usefulness. The purpose of this study was to evaluate 2 of the newer antimuscarinic agents, solifenacin and darifenacin, which demonstrate greater selectivity, in order to compare their tolerance and effectiveness. This was a multicentre, prospective, randomised, comparative (1:1) open-label study conducted in 4 centres comprising Slovenian gynaecologists and urologists. A total of 77 female patients with OAB were enrolled who received either solifenacin 5 mg or darifenacin 7.5 mg once daily. Study measurements consisted of changes in OAB symptoms and quality of life (QOL) evaluations after 1 and 3 months of treatment. Both treatment groups showing a reduction in all OAB symptoms but with no notable difference being seen between the 2 groups. **Solifenacin though showed statistically greater improvements in QOL, better overall treatment satisfaction, and a decreased incidence of dry mouth after 3 months of treatment compared to the darifenacin group.** This study demonstrates interesting initial results and indicates that these 2 drugs have a different profile that may confer an advantage to patients, but further methodologically rigorous studies comparing the use of solifenacin and darifenacin in OAB are required to establish the differences between these drugs over longer periods of treatment.

PMID: 23390832

Botulinum Toxin

- Neurotoxins A – G
- A – Botox and Dysport
- B – Neurobloc and Myobloc
- Binding to nerve terminal
- SNARE / SNAP proteins (essential for vesicular transport) cleaved
- Blocked release of Acetylcholine

Mechanism of Botulinum Toxin

- Botulinum toxin selectively blocks the release of acetylcholine at the pre synaptic nerve terminals
- 3 steps to induce paralysis
  - Bound and internalized in the nerve terminal
  - Light chain is translocated into the cytosol
  - Inhibits neurotransmitter release

Mechanism of Action

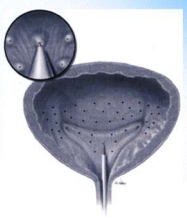
- The effect of botulinum toxin is temporary due to development of collateral axonal sprouts over time
- The sprouts can release Ach into the synaptic space
- The motor end plate eventually regains normal function
- This phenomena explain why we repeat the administration of Botox

Botulinum toxin

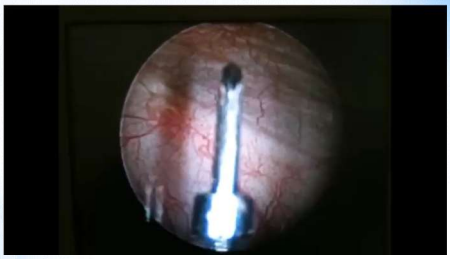
•FDA approval for neurogenic OAB

•Dose and injection technique not clear yet.

•Injection technique not clear
- •Similar effect submucosally and intramuscular
- •Similar effect 10 sites compared to 32 sites

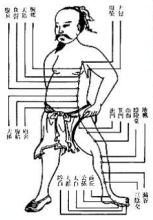


Botulinum toxin



PTNS: Posterior Tibial Nerve Stimulation

PTNS : background



- Known traditional acupuncture point (Sp-6)
  - Bladder
  - L4 S3
  - dermat S2 S3

Neurourology and Urodynamics

Effectiveness of Percutaneous Posterior Tibial Nerve Stimulation for Overactive Bladder: A Systematic Review and Meta-Analysis

C. Burton,* A. Sajja, and P.M. Latthe
Department of Obstetrics & Gynaecology, Birmingham Women's NHS Foundation Trust, Birmingham, United Kingdom

Aim: To evaluate the effectiveness of posterior percutaneous tibial nerve stimulation (PTNS) in treating overactive bladder (OAB) symptoms by systematic review of the literature. **Methods:** Systematic literature search was carried out (up to April 2011) using relevant search terms in Medline, EMBASE, CINAHL, CENTRAL, National Library for Health, MetaRegister of controlled trials, LILACS, and Google Scholar. Relevant randomized controlled trials (RCTs) and prospective studies were selected and then analyzed by two-independent reviewers. Meta-analysis was performed with random effects model using STATA 8 for non-randomized prospective studies and with Review Manager 5.1 for RCTs. **Results:** The studies report variable initial success rates (37–82%) for treating OAB symptoms with PTNS. Four randomized trials compared PTNS with Sham treatment showing a significant difference favoring PTNS [RR 7.02 95% confidence interval (CI) 1.69–29.17]. Two randomized trials compared PTNS with antimuscarinic medication with no significant difference in the change in bladder diary parameters between the treatments. Ten prospective non-randomized studies were included. The definitions of success were varied. The pooled subjective success rate was 61.4% (95% CI 57.5–71.8) and objective success rate was 60.6% (95% CI 49.2–74.7). **Conclusion:** There is evidence of significant improvement in OAB symptoms using PTNS which is comparable to the effect of antimuscarinics but with a better side effect profile. The studies included in the review only considered short-term outcomes after initial treatment. In order to recommend PTNS as a practical treatment option, long-term data and health economic analysis are needed. *Neurourol. Urodynam.* © 2012 Wiley Periodicals, Inc.

Key words: detrusor overactivity; overactive bladder; peripheral neuromodulation; PTNS; SANS; urgency incontinence

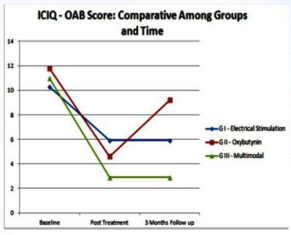
- Perc
  174 c

EAU Guidelines

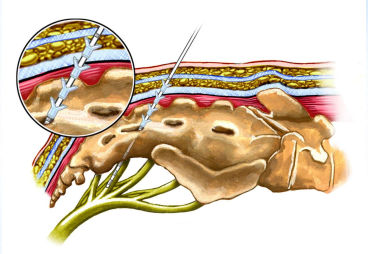
PTNS is effective for improvement of UUI, but not curing UUI in some women who have had no benefit from antimuscarinic medication.	1b
PTNS is no more effective than tolterodine for improvement of UUI in women.	2b
No serious adverse events have been reported for PTNS in UUI.	3

Do not offer PTNS to women or men who are seeking a cure for urgency urinary incontinence	A
Offer, if available, PTNS as an option for improvement of urgency urinary incontinence in women, but not men, who have not benefited from antimuscarinic medication.	B

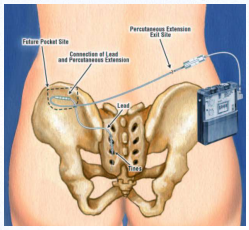
PTNS



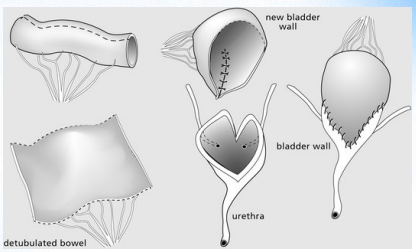
Sacral nuromodulation



Sacral nuromodulation



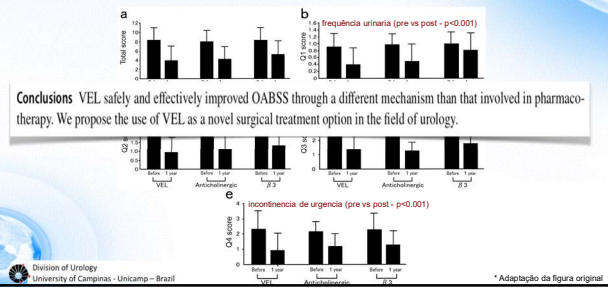
Bladder augmentation



OAB

- What´s new?

LASER

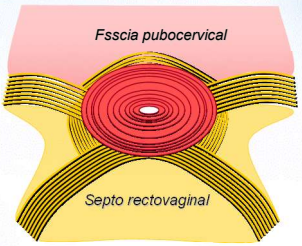


Conclusions VEL safely and effectively improved OABSS through a different mechanism than that involved in pharmacotherapy. We propose the use of VEL as a novel surgical treatment option in the field of urology.

Division of Urology
University of Campinas - Unicamp – Brazil

* Adaptação da figura original

Urgency & pericervical ring



Division of Urology
University of Campinas - Unicamp – Brazil

World Journal of Urology
https://doi.org/10.1007/s00345-019-02644-7
Published online: 28 January 2019

ORIGINAL ARTICLE

Efficacy and safety of non-ablative vaginal erbium:YAG laser treatment as a novel surgical treatment for overactive bladder syndrome: comparison with anticholinergics and β3-adrenoceptor agonists

Nobuo Okui[1]

Table 1 Basic characteristics of the three groups *

	VEL group	Anticholinergics group	β3 group
No. of enrolments	50	50	50
No. of individuals observed for 1 year	50	50	50
Age at beginning of the treatment (years)	63.8 ± 2.56	63.9 ± 2.76	65.32 ± 2.28
OAB disease duration (years)	2.68 ± 0.81	2.41 ± 0.67	2.75 ± 1.74
No. of deliveries	1.98 ± 1.02	1.7 ± 0.7	1.56 ± 0.64
Body mass index (kg/m^2)	24.9 ± 1.38	25.3 ± 1.59	25.2 ± 1.38
Maximum blood pressure (mmHg)	115.5 ± 16.4	114.5 ± 18.4	116.0 ± 14.3
Lowest blood pressure (mmHg)	80.3 ± 12.8	81.1 ± 13.0	80.0 ± 14.4
Blood glucose (mg/dL)	98.1 ± 16.0	97.0 ± 18.0	99.0 ± 17.2
Hemoglobin A1c (%)	5.5 ± 0.29	5.5 ± 0.31	5.5 ± 0.32
No. of individuals with ≥ 100 ml residual urine	0	0	0
No. of individuals who desired other treatment after completion of the observation period	1	2	2
Vaginal Health Index Scale (VHIS)	10.52 ± 1.27	10.34 ± 0.84	10.18 ± 0.94

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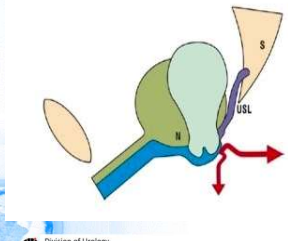
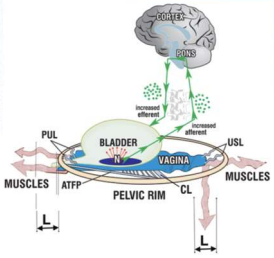
* Adaptação da tabela original

Urgency & pericervical ring

Posterior fornix syndrome





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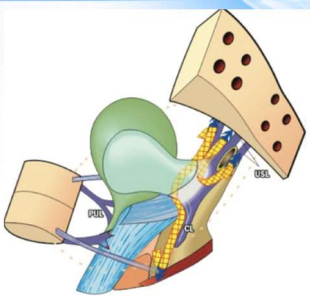
Urgency & pericervical ring

Management of posterior fornix syndrome

Neoligament at level I (Cardinal sacrouterine complex)



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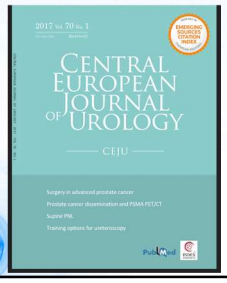
Surgical management of urgency in women



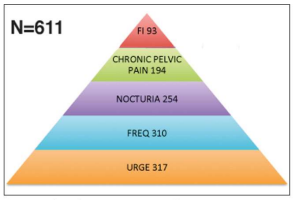


Figure 3. *The Pelvic Symptom pyramid – Symptoms occur in predictable groupings. The Relationship of symptoms within this grouping of 611 patients who had cardinal/uterosacral ligament laxity is expressed as a pyramid.*

Surgial management of urgency

At 12 months following TFS surgery

The anatomical recurrence of vaginal prolapse was 63/611 (10%) after 12 months. There was a significant improvement in all symptoms: (cure/improvement in brackets): urge incontinence (85%), frequency (83%), nocturia (68%), fecal incontinence (65%) chronic pelvic pain (77%) (Table 1).

Combined pharmacological and behavioural treatment

"Whether drug and behavioral therapy are combined from the onset or used sequentially in a stepped program, the evidence from the present study is that two interventions combined have a greater potential to enhance outcome than could be achieved by either intervention alone."

Was partly confirmed in a recent Cochrane review

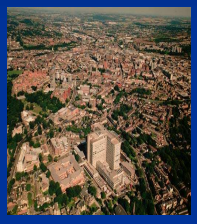
Burgio et al. *J Am Geriatr Soc.* 2000;48:370-374.

Rai et al. *Cochrane reviews.* 2012;vol 12.

Take home messages

- **Urgency is the primary and is the most bothersome symptom that leads to the others.**
- **Effective management of the urgency means effective management of OAB**

Lets Clarify Underactive Bladder: (A Reality or Modern Day Hype??)



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UK

The University Of Sheffield.
Sheffield Hallam University
Sheffield Teaching Hospitals NHS

Disclosures

- Consultant for:-
- Allergan, Astellas, Pfizer and Recordati, Targis, Urovant, Symimetic.
- Researcher, Speaker and Trial Participant for:-
- Allergan, Astellas, Pfizer and Recordati.

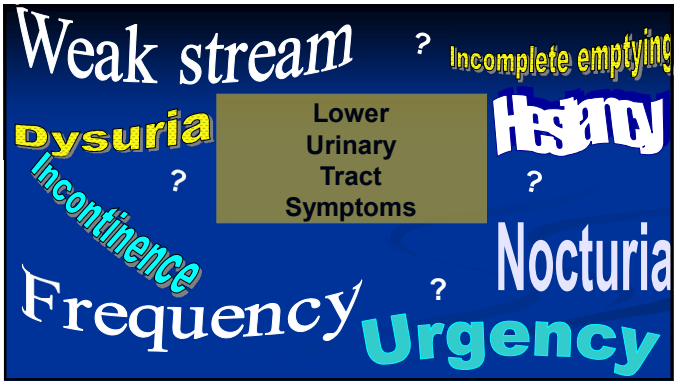
Neurourology and Urodynamics 21:167–178 (2002)
DOI 10.1002/nau.10052

The Standardisation of Terminology of Lower Urinary Tract Function: Report from the Standardisation Sub-committee of the International Continence Society

Paul Abrams, Linda Cardozo, Magnus Fall, Derek Griffiths, Peter Rosier, Ulf Ulmsten, Philip van Kerrebroeck, Arne Victor, and Alan Wein

•Need to consider:-

•SYMPTOMS as reported by the patient
•SIGNS as observed by the clinician
•URODYNAMIC findings as observed during urodynamic studies
•CONDITIONS –urodynamics +symptoms/signs
•TREATMENT based on the above

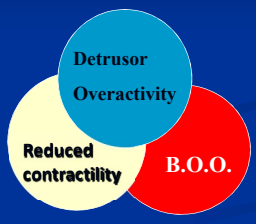


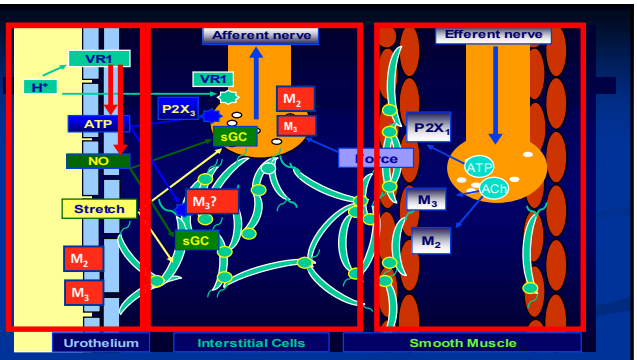
"The Bladder is an Unreliable Witness"[1]

- The bladder
  - Symptoms are not disease-specific
- The patient
  - Difficulties in reporting symptoms
    - Embarrassment
    - Underestimate seriousness: "normal part of aging"
    - Lack of knowledge or low expectation of treatment
- The clinician
  - Clinical skills: failure to elicit specific history
  - Bias, variations in practice and knowledge

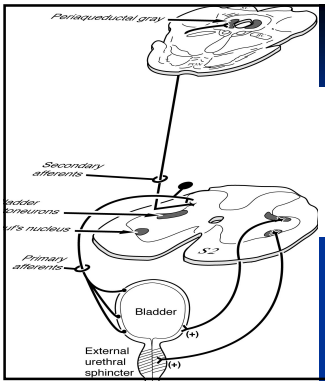
[1] *Turner Warwick 1979 Urol Clin N America*

Patho-physiology of LUTS

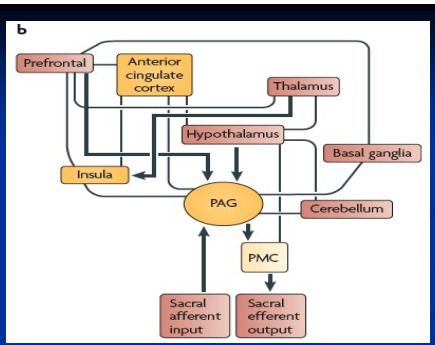




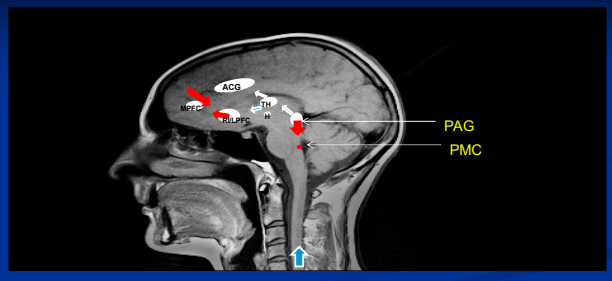
KE Andersson

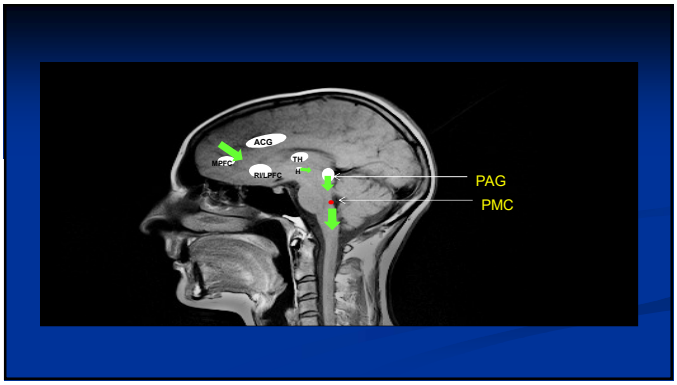


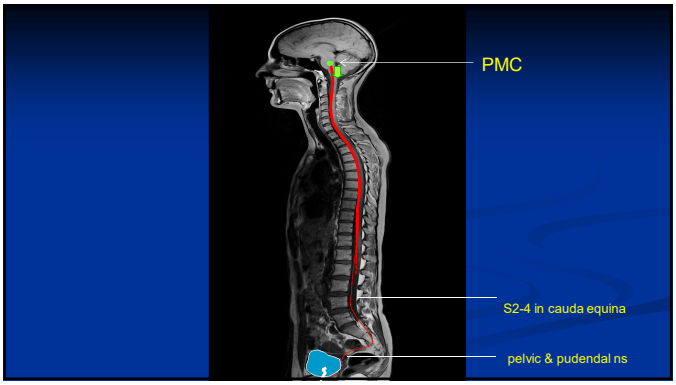
Disturbances or defects could occur at multiple sites: CNS control, sensory nerves, motor nerves and smooth muscle activity

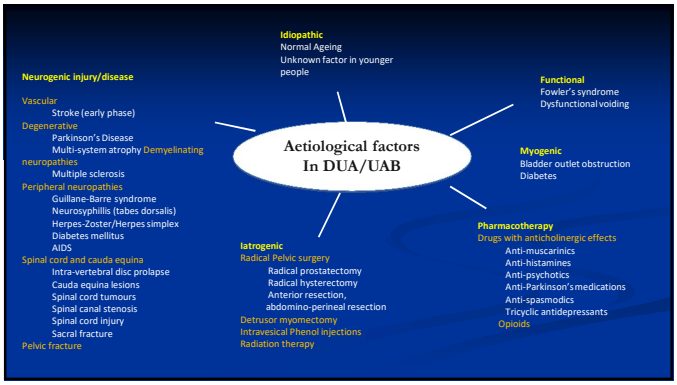


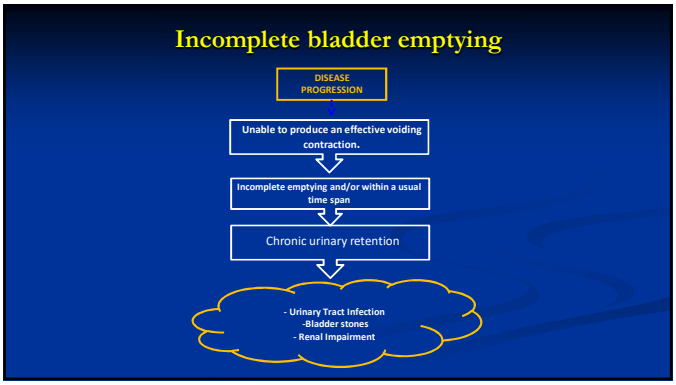
Fowler, de Groat and Griffith, 2008

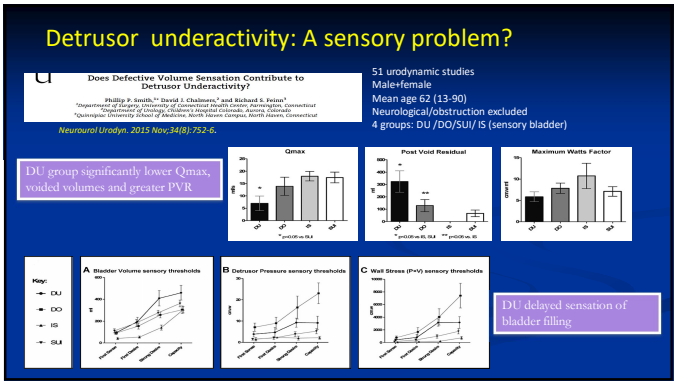


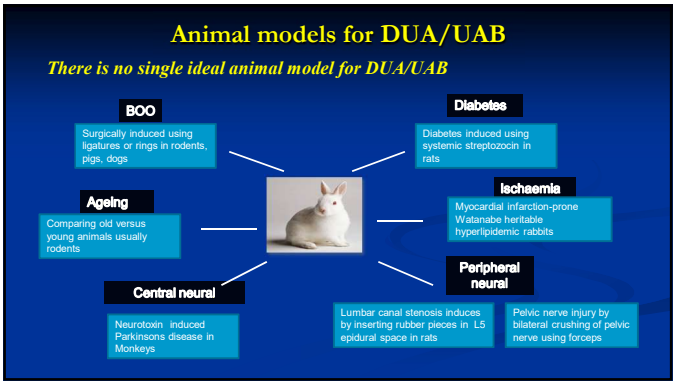

ACG
MPFC
RVLPFC
TH
PAG
PMC

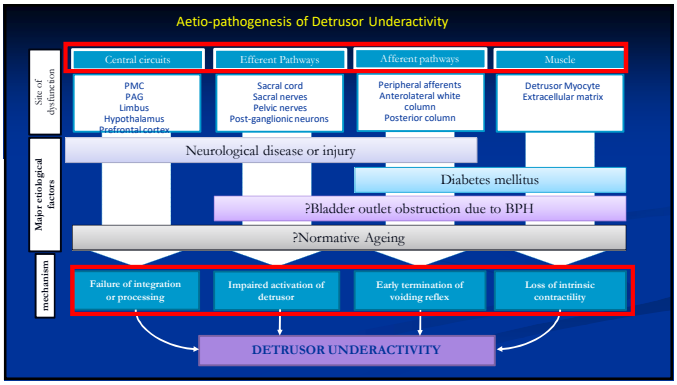

PMC
S2-4 in cauda equina
pelvic & pudendal ns

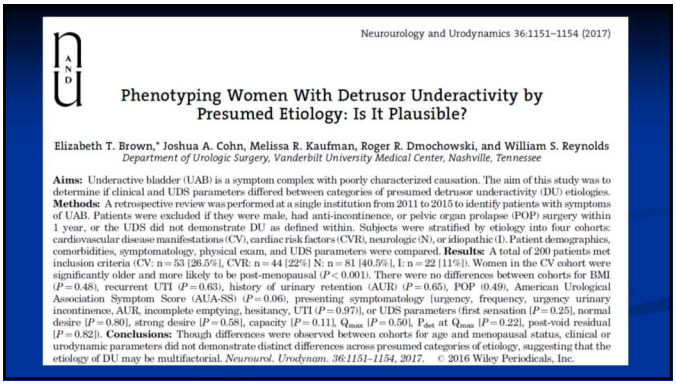

Aetiological factors
In DUA/UAB
Idiopathic
Normal Ageing
Unknown factor in younger people
Functional
Fowler's syndrome
Dysfunctional voiding
Myogenic
Bladder outlet obstruction
Diabetes
Pharmacotherapy
Drugs with anticholinergic effects
Anti-muscarinics
Anti-histamines
Anti-psychotics
Anti-Parkinson's medications
Anti-spasmodics
Tricyclic antidepressants
Opioids
Iatrogenic
Radical Pelvic surgery
Radical prostatectomy
Radical hysterectomy
Anterior resection, abdomino-perineal resection
Detrusor myomectomy
Intravesical Phenol injections
Radiation therapy
Neurogenic injury/disease
Vascular
Stroke (early phase)
Degenerative
Parkinson's Disease
Multi-system atrophy
Demyelinating neuropathies
Multiple sclerosis
Peripheral neuropathies
Guillane-Barre syndrome
Neurosyphillis (tabes dorsalis)
Herpes-Zoster/Herpes simplex
Diabetes mellitus
AIDS
Spinal cord and cauda equina
Intra-vertebral disc prolapse
Cauda equina lesions
Spinal cord tumours
Spinal canal stenosis
Spinal cord injury
Sacral fracture
Pelvic fracture


Incomplete bladder emptying
DISEASE PROGRESSION
Unable to produce an effective voiding contraction.
Incomplete emptying and/or within a usual time span
Chronic urinary retention
- Urinary Tract Infection
-Bladder stones
- Renal Impairment


Detrusor underactivity: A sensory problem?
Does Defective Volume Sensation Contribute to Detrusor Underactivity?
Neurourol Urodyn. 2015 Nov;34(8):752-6.
51 urodynamic studies
Male+female
Mean age 62 (13-90)
Neurological/obstruction excluded
4 groups: DU /DO/SUI/ IS (sensory bladder)
DU group significantly lower Qmax, voided volumes and greater PVR
Qmax
Post Void Residual
Maximum Watts Factor
DU delayed sensation of bladder filling


Animal models for DUA/UAB
There is no single ideal animal model for DUA/UAB
BOO
Surgically induced using ligatures or rings in rodents, pigs, dogs
Diabetes
Diabetes induced using systemic streptozocin in rats
Ageing
Comparing old versus young animals usually rodents
Ischaemia
Myocardial infarction-prone Watanabe heritable hyperlipidemic rabbits
Central neural
Neurotoxin induced Parkinsons disease in Monkeys
Peripheral neural
Lumbar canal stenosis induces by inserting rubber pieces in L5 epidural space in rats
Pelvic nerve injury by bilateral crushing of pelvic nerve using forceps



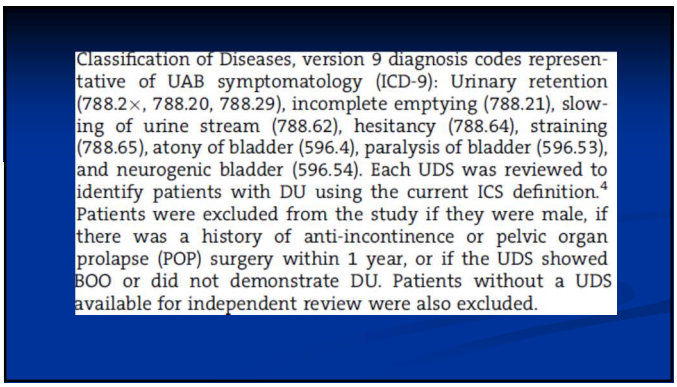


Neurourology and Urodynamics 36:1151–1154 (2017)

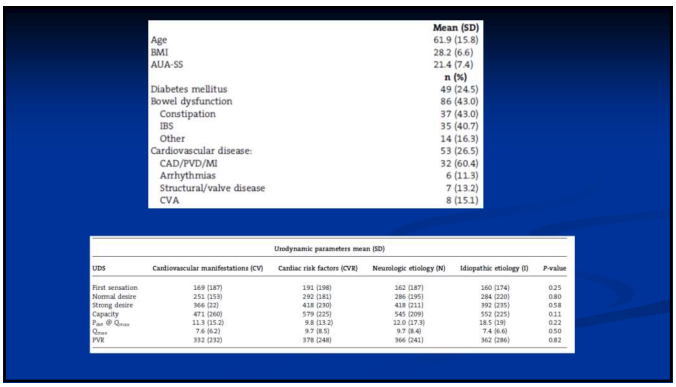
Phenotyping Women With Detrusor Underactivity by Presumed Etiology: Is It Plausible?

Elizabeth T. Brown,* Joshua A. Cohn, Melissa R. Kaufman, Roger R. Dmochowski, and William S. Reynolds
Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, Tennessee

Aims: Underactive bladder (UAB) is a symptom complex with poorly characterized causation. The aim of this study was to determine if clinical and UDS parameters differed between categories of presumed detrusor underactivity (DU) etiologies. **Methods:** A retrospective review was performed at a single institution from 2011 to 2015 to identify patients with symptoms of UAB. Patients were excluded if they were male, had anti-incontinence, or pelvic organ prolapse (POP) surgery within 1 year, or the UDS did not demonstrate DU as defined within. Subjects were stratified by etiology into four cohorts: cardiovascular disease manifestations (CV), cardiac risk factors (CVR), neurologic (N), or idiopathic (I). Patient demographics, comorbidities, symptomatology, physical exam, and UDS parameters were compared. **Results:** A total of 200 patients met inclusion criteria (CV: n = 53 [26.5%], CVR: n = 44 [22%] N: n = 81 [40.5%], I: n = 22 [11%]). Women in the CV cohort were significantly older and more likely to be post-menopausal ($P < 0.001$). There were no differences between cohorts for BMI ($P = 0.48$), recurrent UTI ($P = 0.63$), history of urinary retention (AUR) ($P = 0.65$), POP (0.49), American Urological Association Symptom Score (AUA-SS) ($P = 0.06$), presenting symptomatology [urgency, frequency, urgency urinary incontinence, AUR, incomplete emptying, hesitancy, UTI ($P = 0.97$)], or UDS parameters (first sensation [$P = 0.25$], normal desire [$P = 0.80$], strong desire [$P = 0.58$], capacity [$P = 0.11$], Q_{max} [$P = 0.50$], P_{det} at Q_{max} [$P = 0.22$], post-void residual [$P = 0.82$]). **Conclusions:** Though differences were observed between cohorts for age and menopausal status, clinical or urodynamic parameters did not demonstrate distinct differences across presumed categories of etiology, suggesting that the etiology of DU may be multifactorial. *Neurourol. Urodynam. 36:1151–1154, 2017.* © 2016 Wiley Periodicals, Inc.



Classification of Diseases, version 9 diagnosis codes representative of UAB symptomatology (ICD-9): Urinary retention (788.2×, 788.20, 788.29), incomplete emptying (788.21), slowing of urine stream (788.62), hesitancy (788.64), straining (788.65), atony of bladder (596.4), paralysis of bladder (596.53), and neurogenic bladder (596.54). Each UDS was reviewed to identify patients with DU using the current ICS definition.[4] Patients were excluded from the study if they were male, if there was a history of anti-incontinence or pelvic organ prolapse (POP) surgery within 1 year, or if the UDS showed BOO or did not demonstrate DU. Patients without a UDS available for independent review were also excluded.



	Mean (SD)
Age	61.9 (15.8)
BMI	28.2 (6.6)
AUA-SS	21.4 (7.4)
	n (%)
Diabetes mellitus	49 (24.5)
Bowel dysfunction	86 (43.0)
Constipation	37 (43.0)
IBS	35 (40.7)
Other	14 (16.3)
Cardiovascular disease:	53 (26.5)
CAD/PVD/MI	32 (60.4)
Arrhythmias	6 (11.3)
Structural/valve disease	7 (13.2)
CVA	8 (15.1)

Urodynamic parameters mean (SD)

UDS	Cardiovascular manifestations (CV)	Cardiac risk factors (CVR)	Neurologic etiology (N)	Idiopathic etiology (I)	*P*-value
First sensation	169 (187)	191 (198)	162 (187)	160 (174)	0.25
Normal desire	251 (159)	292 (181)	286 (195)	284 (220)	0.80
Strong desire	366 (22)	418 (230)	418 (211)	392 (235)	0.58
Capacity	471 (260)	579 (225)	545 (209)	552 (225)	0.11
P_{det} @ Q_{max}	11.3 (15.2)	9.8 (13.2)	12.0 (17.3)	18.5 (19)	0.22
Q_{max}	7.6 (6.2)	9.7 (8.5)	9.7 (8.4)	7.4 (6.6)	0.50
PVR	332 (232)	378 (248)	366 (241)	362 (286)	0.82

Terminology

"When I use a word…It means just what I choose it to mean-neither more nor less"

- Detrusor areflexia
- Atonic bladder
- Desensate bladder
- Detrusor or bladder failure
- Underactive bladder/detrusor
- Chronic retention
- Detrusor underactivity (DUA) (ICS 2002)

Neurourology and Urodynamics 21:167–178 (2002)
DOI 10.1002/nau.10052

The Standardisation of Terminology of Lower Urinary Tract Function: Report from the Standardisation Sub-committee of the International Continence Society

Paul Abrams, Linda Cardozo, Magnus Fall, Derek Griffiths, Peter Rosier, Ulf Ulmsten, Philip van Kerrebroeck, Arne Victor, and Alan Wein

Detrusor Underactivity (DU) and Underactive Bladder (UAB)

- DU is diagnosed urodynamically and has an ICS definition
  - Based on pressure-flow
  - Characterized by low-pressure, and/or poorly sustained detrusor contraction in combination with low urinary flow
- UAB has not had an ICS definition
  - "The clinical syndrome that accompanies DU"

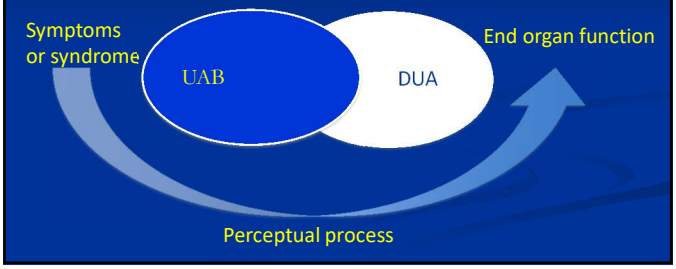
Andersson KE:. Curr Opin Urol. 2014

Need for a UAB definition?

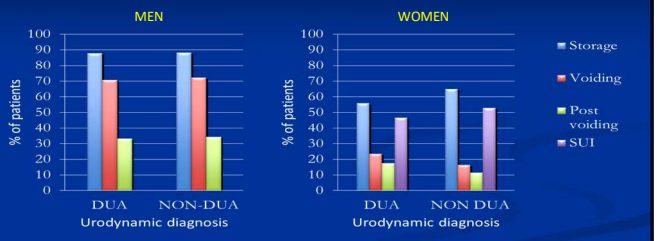
UAB could be to DU, as OAB is to DO?

If drug treatment becomes available, patients will need to be identified without pressure-flow diagnosis.

Is UAB synonymous with DUA ?

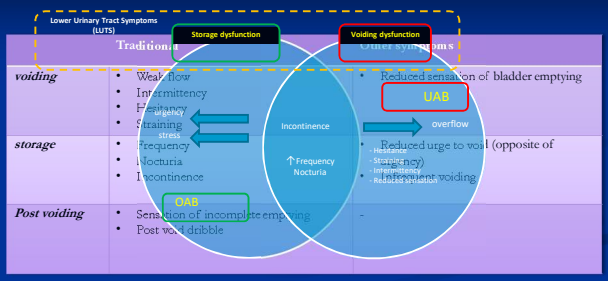


Symptoms associated with DUA



Jeong SJ, Kim HJ, Lee YJ, Lee JK, Lee BK, Choo YM, Oh JJ, Lee SC, Jeong CW, Yoon CY, Hong SK, Byun SS, Lee SE. Prevalence and Clinical Features of Detrusor Underactivity among Elderly with Lower Urinary Tract Symptoms: A Comparison between Men and Women. Korean J Urol. 2012 May;53(5):342-8.

Symptoms associated with DUA



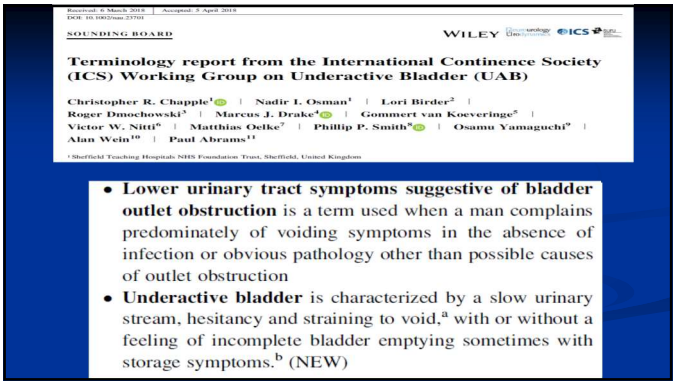
Proposed Definition

Underactive bladder is characterised by a slow urinary stream, hesitancy and straining to void *, with or without a feeling of incomplete bladder emptying and dribbling, often with storage symptoms**.

- * *Underactive bladder occurs in association with diverse pathophysiologies and based on current knowledge there is no single distinguishing symptom.*
- ** *Storage symptoms are varied and may be highly prevalent, including nocturia, increased daytime frequency, reduced sensation of filling and incontinence. Underlying mechanisms of storage symptoms are diverse, and are often related to a significant post voiding residual urine volume.*

Chapple CR, Osman NI, Birder L, van Koeveringe GA, Oelke M, Nitti VW, Drake MJ, Dmochowski R, Yamaguchi O, Abrams P, Smith PP, Wein A.

- Associated factors
  - Gender
  - Age
  - Neurogenic versus Non-Neurogenic
- Associated Investigation
  - Bladder Diary
  - Flow rate/ Post Void Residuals
  - Pressure/Flow Urodynamics



SOUNDING BOARD

WILEY

Terminology report from the International Continence Society (ICS) Working Group on Underactive Bladder (UAB)

Christopher R. Chapple[1] | Nadir I. Osman[1] | Lori Birder[2] | Roger Dmochowski[3] | Marcus J. Drake[4] | Gommert van Koeveringe[5] | Victor W. Nitti[6] | Matthias Oelke[7] | Phillip P. Smith[8] | Osamu Yamaguchi[9] | Alan Wein[10] | Paul Abrams[11]

[1] Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

- **Lower urinary tract symptoms suggestive of bladder outlet obstruction** is a term used when a man complains predominately of voiding symptoms in the absence of infection or obvious pathology other than possible causes of outlet obstruction
- **Underactive bladder** is characterized by a slow urinary stream, hesitancy and straining to void,[a] with or without a feeling of incomplete bladder emptying sometimes with storage symptoms.[b] (NEW)

Signs and Symptoms of Detrusor Underactivity: An Analysis of Clinical Presentation and Urodynamic Tests From a Large Group of Patients Undergoing Pressure Flow Studies

Andrew Gammie[a,], Mathilde Kaper[b], Caroline Dorrepaal[b], Ton Kos[b], Paul Abrams[a]*

[a]Bristol Urological Institute, Southmead Hospital, Bristol, UK; [b]Astellas Pharma Europe B.V., Leiden, The Netherlands

-Retrospective analysis
-Prospective database
-1788 patients (men+women)

Confirms symptoms associated with DUA

Men		Women	
Higher occurrence for DU vs normal PFS	Higher occurrence for DU vs BOO	Higher occurrence for DU vs normal PFS	Higher occurrence for DU vs BOO
Decreased urinary stream	Abnormal sexual function	Decreased urinary stream	Decreased urinary stream
Interrupted urinary stream	Stress incontinence	Interrupted urinary stream	Stress incontinence
Hesitancy	Enuresis	Hesitancy	Enuresis
Incomplete bladder emptying	Palpable bladder	Incomplete bladder emptying	Absent and/or decreased sensation
Palpable bladder	Absent and/or decreased sensation	Palpable bladder	
Absent and/or decreased sensation	Always strain to void	Absent and/or decreased sensation	
Always strain to void	Bowel strain	Enuresis	
Incomplete bowel emptying	Incomplete bowel emptying	Impaired mobility	
	Poor bowel control		
Lower occurrence for DU vs normal PFS	Lower occurrence for DU vs BOO	Lower occurrence for DU vs normal PFS	Lower occurrence for DU vs BOO
None	Decreased urinary stream	None	None
	Hesitancy		
	Urgency		

Suggest some symptoms may differentiate DUA from BOO

Eur Urol. 2016 Feb;69(2):361-9.

The patient experience of underactive bladder

A. Uren[1], N. Cotterill[1], C. Harding[2], C. Hillary[3], C. Chapple[3], M. Klaver[4], D. Bongaerts[4], Z. Hakimi[4], P. Abrams[1]
[1]British Urological Institute, UK; [2]Freeman Hospital, Newcastle; [3]Royal Hallamshire Hospital, Sheffield; [4]Astellas Pharma B.V., Leiden, The Netherlands.

Background

- Detrusor underactivity (DU) is a common but poorly understood lower urinary tract dysfunction, diagnosed following urodynamic testing.
- The working definition of underactive bladder (UAB) is currently proposed as :

> *"A symptom complex suggestive of detrusor underactivity and is usually characterised by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream."*
> *Chapple CR, Osman NI, Birder L, van Koeveringe GA, Oelke M, Nitti VW, Drake MJ, Yamaguchi O, Abrams P, Smith PP. The underactive bladder: a new clinical concept? Eur Urol. 2015 Sep;68(3):351-3.*

Methods

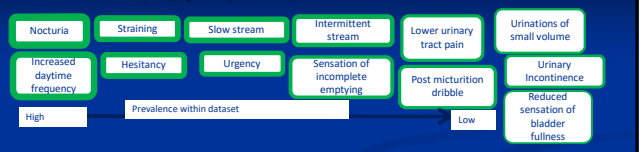
- 47 concept elicitation interviews conducted (32 male, 15 female, mean age 64 years)

In-depth, semi-structured interviews → Qualitative analysis of the transcripts → 1st version of the PRO generated

Abstract 995 EAU 2016

Results

- More than 30 symptoms, signs or impacts were reported.



Sample or diagnostic group	Total number of patients n	Males n (%)	Females n (%)	Mean age and range (years)	Currently or historically self-catheterised n (%)	Urodynamically confirmed PVR n (%)
DU (only)	19	12 (63%)	7 (37%)	59 (27-88)	10 (53%)	15 (79%)
DU with other co-existing urological conditions (DO, BOO, BOO-E, SUI)	25	17 (68%)	8 (32%)	68 (38-87)	13 (52%)	20 (80%)
BOO	3	3 (100%)	0 (0%)	67 (64-72)	0 (0%)	1 (33%)

Abstract 995 EAU 2016

Neurourol Urodyn. 2019 Mar;38(3):996-1004. doi: 10.1002/nau.23947. Epub 2019 Feb 22.

The development of the ICIQ-UAB: A patient reported outcome measure for underactive bladder.

Uren AD[1], Cotterill N[1], Harding C[2], Hillary C[3], Chapple C[3], Lasch K[4], Stroupe A[4], Deshpande C[5], Delbecque L[6], Van Koeveringe G[7], Oelke M[8], Belal M[9], Bosch R[10], Blok B[11], Nitti V[12], Gotoh M[13], Takei M[14], Crawford B[15], Klaver M[16], Bongaerts D[16], Hakimi Z[16], Kos T[16], Abrams P[1].

Author information

Abstract

AIMS:
To present the development of the International Consultation on Incontinence Questionnaire-underactive bladder (ICIQ-UAB) as the first patient reported outcome measure for the assessment of the symptoms and impact on the health-related quality of life of UAB developed in-line with the Food and Drug Administration Guidance for Industry.

METHODS:
Draft items were developed following 44 semi-structured concept elicitation interviews in the UK and refined using 36 cognitive interviews. A pilot study was designed to assess the draft ICIQ-UAB's initial psychometric properties with 54 patients recruited from European hospitals. Further concept elicitation interviews were also carried out with 11 patients in the US and 10 patients in Japan. All participants had a prior urodynamic diagnosis of detrusor underactivity.

RESULTS:
The cognitive interviews confirmed the initial items to be understood and interpreted as intended. Pilot testing showed that both internal consistency (Cronbach's α ≥ 0.85) and test-retest reliability (stable patients; intraclass correlation coefficient ≥ 0.88) were high. The interviews in the US and Japan elicited symptoms and impacts that support previous findings in the UK and provided further insight into the experiences of patients in those countries. The developmental ICIQ-UAB was refined using the evidence from all substudies.

CONCLUSIONS:
The validity and reliability of the ICIQ-UAB were supported in a pilot study setting and the wider cultural applicability by the additional interviews in the US and Japan. Following further validation in future clinical trials, the developmental ICIQ-UAB is envisaged as an important tool for the monitoring of future UAB treatment strategies.

Refining the definition

There needs to be:

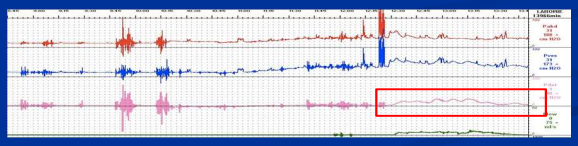
- Qualitative research to look for characteristic symptoms
- Quantitative research in urodynamically defined DU patients

Normal Detrusor Function
ICS Definition 2002

- Normal voiding is achieved by a voluntarily initiated continuous detrusor contraction that leads to complete bladder emptying within a normal time span, and in the absence of obstruction
- For a given detrusor contraction, the magnitude of the recorded pressure rise will depend on the degree of outlet resistance

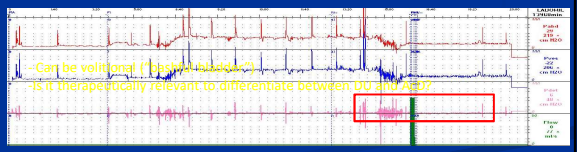
DU - ICS Definition (2002)

" A contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span"



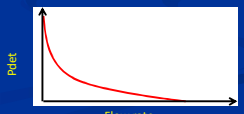
Acontractile detrusor (AcD) – ICS (2002)

" (a detrusor) that cannot be demonstrated to contract during urodynamic studies"



Urodynamic assessment of bladder voiding function: Key points

- Most measures of detrusor voiding function assess only strength of contraction rather than sustainability or speed of contraction
- 2 parameters used to estimate strength: Qmax and Pdet@Qmax
- Urodynamic estimation of isometric contraction strength based on Bladder outlet relation (BOR) (Griffiths 1972)

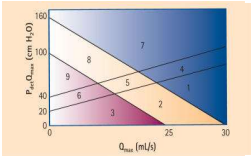


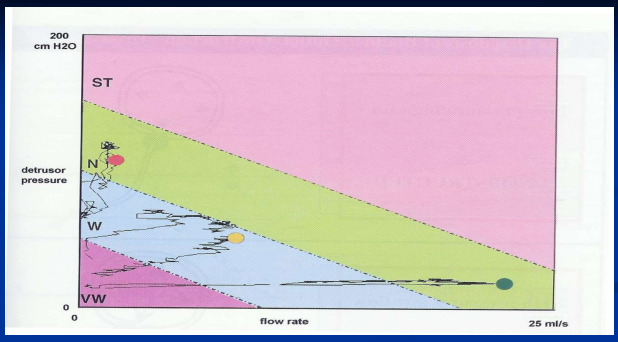
The Bladder Outflow Obstruction Index (BOOI)

Most authors use ranges for *Pdet@Qmax (e.g. <40)* and *Qmax* (e.g. <15)

BOOI (Abrams Griffiths Number)
Pdet.Qmax -2xQmax

Unobstructed :- </= 20 cmH_2O
Equivocal </= 20-40 cmH_2O
Obstructed >/=40 cmH_2O

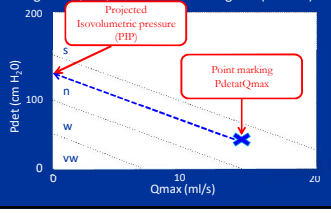




Assessing bladder voiding function: Strength

Projected isolvolumetric pressure (PIP) and its derivations detrusor coefficient (DECO) and Bladder contractility index (BCI)]

Simplified method of estimating isometric contraction strength by drawing the BOR (simplified to straight line) on pressure flow nomogram (Schäfer)



PIP can be calculated using formula:

PIP= Pdet@Qmax + kQmax,

K-fixed constant, represents slope of BOR
in older men = 5cmH2O/ml/s /(?2-3cmH2O)
(in older women 1cmH2O/ml/s)

>150 strong contractility
100-150 normal contractility
50-100 weak contractility
<50 very weak contractility

Assessing bladder voiding function: Strength

Projected isolvolumetric pressure (PIP) and its derivations [detrusor coefficient (DECO) and Bladder contractility index (BCI)]

Schäfer's simplified method of estimating isometric contraction strength based on drawing the BOR on (Schäfer's) pressure flow nomogram

BCI
Strong>150
Normal 100-130
Weak <100

Advantages:-
- Simple to use
- Measurement easy to obtain
- Estimation of isovolumetric contraction

Limitations:-
- May not be applicable to other groups (e.g. men with PPI)
- Poorer test-retest reliability than stop tests

ORIGINAL CLINICAL ARTICLE
WILEY

Comparison of three methods to analyze detrusor contraction during micturition in men over 50 years of age

Celine ten Donkelaar S MD | Peter Rosier FWM, MD, PhD | Laetitia de Kort MO, MD, PhD

Aims: To grade detrusor voiding contraction three parameters are used: the Schäfer pressure-flow nomogram (LinPURR), the bladder contractility index (BCI) and the maximum Watt factor (W_{max}). Because these methods to quantify detrusor contraction and/or to diagnose detrusor underactivity (DU) have not yet been mutually compared, this study compares these three methods of grading detrusor contraction.

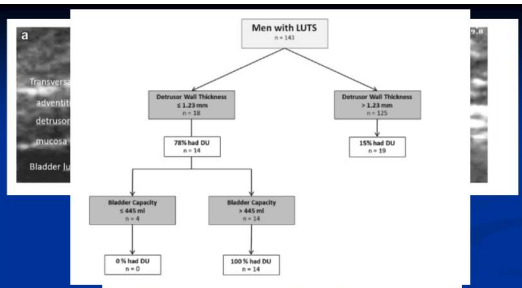
Materials and Methods: Evaluated were 1420 urodynamic pressure-flow studies from 1222 men (aged >50 years) with lower urinary tract symptoms (LUTS). Excluded were patients with abnormal urinalysis, neurological disorders, surgical correction of congenital anomalies, pelvic surgery, post radical prostatectomy, or with evidence of urethral stricture. Contractility was graded with the LinPURR, the BCI, and W_{max}, making a distinction between "strong," "normal," "weak," and "very weak" contractility. We calculated agreement between LinPURR and both BCI and W_{max}.
Results: The contractility groups LinPURR and BCI, as well as LinPURR and W_{max}, showed a high agreement of 97.5% and 80.9%, respectively.

World J Urol (2017) 35:153–159
DOI 10.1007/s00345-016-1902-7
CrossMark
ORIGINAL ARTICLE

Ultrasound detrusor wall thickness measurement in combination with bladder capacity can safely detect detrusor underactivity in adult men

Kevin L. J. Rademakers[1] · Gommert A. van Koeveringe[1] · Matthias Oelke[2] · on behalf of the FORCE Research Group, Maastricht and Hannover

Results The study population consisted of 143 consecutive men with medians of 62 years, IPSS 16, and prostate volume 35 ml. In total, 33 patients (23.1 %) had DU. CART analysis showed that all men with DWT ≤ 1.23 mm plus bladder capacity >445 ml had DU. This multivariate model has a sensitivity of 42 %, specificity of 100 %, positive predictive value of 100 %, and negative predictive value of 85 %.



Conclusions This study showed that all men with ultrasound DWT ≤ 1.23 mm + bladder capacity >445 ml have DU. Combination of these two tests could help physicians to diagnose DU noninvasively in clinical practice. A prospective independent study should confirm these results.

Assessing bladder voiding function: Strength

Occlusion tests

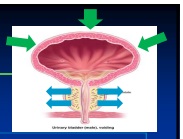
Isovolumetric pressure can be measured directly by mechanically obstructing the flow of urine

(1) Stop test: interruption of urine flow after it has begun (voluntary or mechanical)
(2) Continuous occlusion test: urine outflow blocked before and during the course of the voiding contraction.

Advantages:-
- Real time indication of isovolumetric strength
- Good test retest reliability
- No calculations

Limitations:-
- Impractical and painful and impossible in some patients
- Can underestimate contraction strength (voluntary stop test)
- Need to repeat voiding phase (continuous occlusion)

Interventions for DUA/UAB



Bladder Related (Increasing intravesical pressure or facilitating bladder contractility)
- External compression, Valsalva
- Promotion / initiating reflex contraction
- Pharmacologic therapy
- Electrical stimulation
- Reduction cystoplasty
- Bladder myoplasty

Outlet Related (Decreasing outlet resistance)
- At a site of anatomic obstruction
  - Pharmacologic therapy
  - Prostatectomy, prostatotomy
  - Bladder neck incision or resection
  - Urethral stricture repair or dilation
  - Intraurethral stent
  - Balloon dilatation
- At level of smooth sphincter
  - Pharmacologic therapy
  - Transurethral resection or incision
  - Y-V plasty
- At level of striated sphincter
  - Behavioural therapy ± biofeedback
  - Pharmacologic therapy
  - Urethral overdilation
  - Surgical sphincterotomy
  - Urethral stent
  - Pudendal nerve interruption

Circumventing the Problem
- Intermittent catheterisation
- Continuous catheterisation
- Urinary diversion (conduit)

Conservative management

1) Behavioral interventions
- Scheduled voiding
- Double voiding
- Straining

2) Pelvic floor physiotherapy and Biofeedback

3) Catheterisation
- Intermittent self catheterisation
- Indwelling (suprapubic) catheter

Monitoring

- Thomas et al 10-year urodynamic follow up of men diagnosed with DU (Qmax<15ml/s, Pdet@Qmax<40cmH_2O) initially managed with watchful waiting (no catheterisation)
- Sixty-nine men who initially opted for watchful waiting were followed-up with PFS (mean follow up 13.6 years).
- No significant deterioration in symptomatic or urodynamic parameters over time.
- Only eleven patients failed the initial watchful waiting approach and underwent TURP, 8 (11.6%) due to worsening LUTS and 3 (4.35%) due to acute retention.

Thomas AW, Cannon A, Bartlett E, BJU international. 2005 Dec; **96**:1295-300

Monitoring

- Check :-
  - Residuals
  - Biochemistry / Urine Cultures
  - Upper Tracts
  - ? Bladder Wall Thickness

Epidemiology

- **The contribution of DUA to LUTS on a population basis is unknown.**
- **Possible outcome measures:-**

Potential epidemiological measure of DU	For	Against
LUTS	-Feasible to collect large scale data using -questionnaire or surveys	-Commonly found in other LUT dysfunctions. -Impossible to differentiate from BOO.
Free Flow measurement	-Non-invasive and easy to perform -objective data -positive findings in DU	-Does not distinguish DU from BOO.
Post-void Residual	-Non-invasive and easy to perform -objective data	-Poor test-retest reliability -No accepted threshold for abnormal PVR -May not be a constant feature of DU
Urinary retention	-Feasible to collect large scale data	-Variable definitions -No accepted threshold for PVR for Chronic retention -Multifactorial aetiology

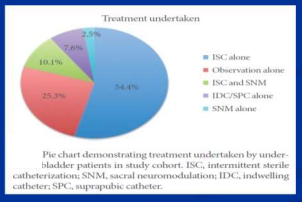
Prevalence of DUA in clinical studies

Study	Population	Size	Age range (yrs)	Prevalence of DU + (% of acontractile detrusors)
Fusco et al 2001		541	26-89	10%
Kuo et al 2007	Male	1407	46-96	10.6%
Nitti et al 2007	Male	85	18-45	8%
Wu				
Kup				
Kar				
Arb				
Jeong et al 2012	Male Female	632 547	>65 >65	40.2% 13.3%
Resnick et al 1989	Male Female	17 77	87+	30%*Male
Resnick et al 1996	Female	97	87.6♦	45%*
Groutz et al 1999	Female	206	62.6±15.8 yrs♦	19%
Valentini et al 2011	Female	442	>55	13.8%

- DUA affects 9-28% of men under the age of 50 years
  48% in those over 70 years undergoing urodynamics
- DUA is found in 12-45% of women undergoing urodynamic studies
  is more prevalent amongst the institutionalized elderly.

Original Article

Underactive Bladder: Clinical Features, Urodynamic Parameters, and Treatment



Pie chart demonstrating treatment undertaken by underbladder patients in study cohort. ISC, intermittent sterile catheterization; SNM, sacral neuromodulation; IDC, indwelling catheter; SPC, suprapubic catheter.

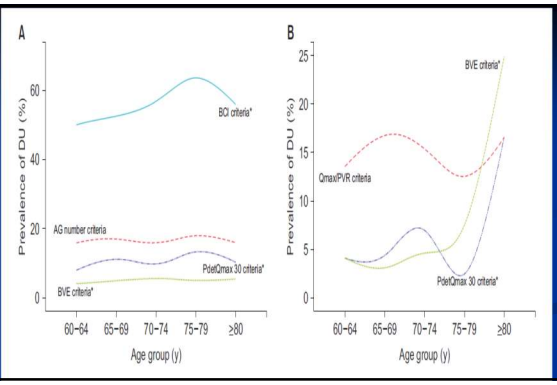
Original Article - Lower Urinary Tract Dysfunction

How do we diagnose detrusor underactivity? Comparison of diagnostic criteria based on an urodynamic measure

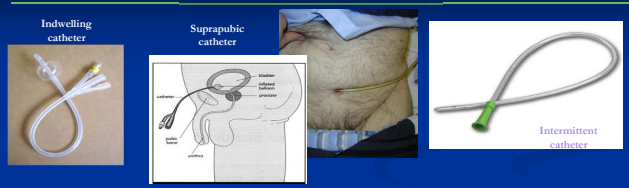
Table 1. Previously proposed urodynamic criteria for diagnosing detrusor underactivity in the literature

Study	Target population	Diagnostic criteria	Byname in the present study
Abrams (1999) [4]	Male	BCI <100	BCI criteria
Nitti et al. (2002) [5]	Male	AG number<20 and free uroflow Qmax<12 mL/s	AG number criteria
Abarbanel and Marcus (2007) [6]	Male	PdetQmax<30 cmH_2O and PFS Qmax<10 mL/s	PdetQmax 30 criteria
Gammie et al. (2016) [8]	Male	BCI<100 and AG number<20 and BVE%<90	BVE criteria
Groutz et al. (1999) [7]	Female	Qmax<12 mL/s with ≥100 mL voided or PVR volume>150 mL on 2 or more free flow readings	Qmax/PVR criteria
Abarbanel and Marcus (2007) [6]	Female	PdetQmax<30 cmH_2O and PFS Qmax<10 mL/s	PdetQmax 30 criteria
Gammie et al. (2016) [8]	Female	PdetQmax<20 cmH_2O and PFS Qmax<15 mL/s and BVE%<90 and absence of clinical obstruction	BVE criteria

BCI, bladder contractility index; AG number, Abrams-Griffith number; Qmax, maximum flow rate; PdetQmax, detrusor pressure at maximal flow rate; PFS, pressure-flow study; BVE, bladder voiding efficiency; PVR, postvoid residual.



Catheterisation



Clean intermittent self-catheterisation:

- Most prevalent method of bladder management in patients with UAB
- Complications rare compared with indwelling/suprapubic catheters
  - UTI, urethral trauma, urethritis, epididymo-orchitis and urethral bleeding
- However, many patients find the technique difficult

Pharmacological agents to facilitate bladder emptying

No effective pharmacotherapy for UAB exists

Increasing intravesical pressure/bladder contractility
- Parasympathetic agents (bethanechol, distigmine)
- Prostaglandins
- Blockers of inhibition
- Opioid receptor antagonists

Decreasing outlet resistance
- α-adrenergic receptor antagonists (phenoxybenzamine, prazosin, terazosin / doxazosin, alfuzosin / tamsulosin, silodosin)
- Benzodiazipines
- Baclofen
- Dantrolene
- Botulinum toxin
- [anti-androgens for reducing prostatic size, e.g. finasteride]

- Available studies do not support the use of parasympathomimetics[1]
  - Specifically when frequent and/or serious possible side effects are taken into account
- Combination therapy with a cholinergic drug and an alpha-blocker appears to be more useful than monotherapy[2]

1. Barendrecht BJU Int 2007;99:749–52; 2. Yamanishi Int J Urol 2004;11:88–96.

Contents lists available at ScienceDirect
Pharmacological Reports
journal homepage: www.elsevier.com/locate/pharep
ELSEVIER
Review article

Pharmacotherapy in detrusor underactivity: A new challenge for urologists and pharmacologists (from lab to clinic)

Kajetan Juszczak *, Tomasz Drewa

ABSTRACT

Higher incidence of functional urinary bladder dysfunction (detrusor overactivity – DO and detrusor underactivity – DU) occurs in elderly people. Effective therapy is widely used in patients with DO, in contrast DU seems to be a serious burden for the older population due to the lack of successful treatment. The aim of the study was to review the potential pharmacological targets in DU treatment in the animal model. This review is based on systemic literature research. The Medline/Pubmed, Scopus, Embase, and Web of Science databases were searched in order to identify original and review articles, as well as editorials relating to underactive bladder, detrusor underactivity. The following Medical Subject

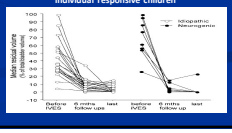
models, humans and therapy. 19 papers met the criteria and were included for this review. 19 papers met the criteria and were included for this review. The pathophysiology of DU and its animal models were described. Moreover, the potential pharmacological targets in DU therapy were discussed, such as bombesin receptors, prostaglandin-, ATP-, NO-, CGRP-, SP-, Dopamine-, NGF-, M2-, and agrin-dependent pathways. In conclusion, due to the lack of effective treatment strategies in DU, further research is necessary. Close cooperation between urologists and pharmacologists should be maintained for optimal research on DU pharmacotherapy.

Intravesical Electrical Stimulation (IVES)

- Establishes conscious control of the initiation and completion of a micturition reflex
- Activates specific mechanoreceptors in the bladder wall
- Lowers the micturition threshold and enhances reflex amplitude
- Randomised placebo-controlled trials lacking

- Achieved long-term normalisation of voiding in 20/24 (83%) children with idiopathic, and 8/20 (40%) with neurogenic, underactive detrusor[1]
  - 10 daily 60 min session (5 b.i.d 20 min sessions in 22 pts) followed by home treatment (2–3 times weekly) until bladder function normalised/no further improvement
  - In responsive children (at 6 months):
    - median residual volume decreased (**75 mL** (range 6–419) to **22 mL** (range 0–338); p<0.0001)
    - median voided volume increased (**80 mL** (range 0–625) to **220 mL** (range 30–636); p<0.0001)
  - Effects stable for 2 years
  - Catheterisation discontinued in 11/15 cases

IVES induced change in residual urine volume of individual responsive children[1]

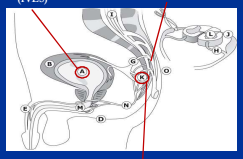


1. Glaab Neurourol Urodyn 2003;22:231–42.

Electrical stimulation

Intravesical stimulation (IVES)

Brindley device (S2, S3, S4 nerve roots)



Sacral nerve modulation
- Used for idiopathic urinary retention

Brindley device[1]
- Ventral root stimulation +/- dorsal root section / sacral deafferentiation
- Requires intact neural pathway and a bladder capable of contracting (generally used for SCI patients)
- Post-stimulus voiding:
  - Relaxation time of striated sphincter is shorter than the relaxation time of the detrusor smooth muscle
- Limitations: Voiding may occur in spurts at above-normal bladder pressures

Sacral nerve modulation
- In patients with retention (n=31)[2], achieved decrease in:
  - mean volume per catheterisation (379.9 ±183.8 to 109.2 ±184.3 mL)
  - mean number of catheterisations (5.3 ±2.8 to 1.9 ±2.8)

Effective, but invasive

1. Brindley J Physiol 1974;237:15P–16P; 2. Van Kerrebroek J Urol 2007;178:2029–34; Figure from Gaziel Prog Brain Res 2006;152:163–94. SCI, spinal cord injury.

Neurourology and Urodynamics

Prediction of Sacral Neuromodulation Treatment Success in Men With Impaired Bladder Emptying—Time For a New Diagnostic Approach

Kevin L. Rademakers,[1,2,3]* Jamie M. Drossaerts,[1,3] Philip E. van Kerrebroeck,[1,3] Matthias Oelke,[2,4] and Gommert A. van Koeveringe[1,2,3]
[1]Department of Urology, Maastricht University Medical Centre, Maastricht, The Netherlands
[2]FORCE Research Group Maastricht and Hannover
[3]School for Mental Health and Neuroscience MHeNs, Maastricht, The Netherlands
[4]Department of Urology, Hannover Medical School, Hannover, Germany

Methods and Evidence: The aim of this study was to assess whether the use of the new BOO-contractility (Maastricht-Hannover) nomogram can identify and predict SNM non-responders. Our results in 18 men showed that only 20% of patients below the 10th percentile, but 86% of men between the 10 and 25th percentiles of the nomogram can be treated successfully with SNM. All successfully treated patients voided without needing self- catheterisation. **Conclusions:** This pilot study showed for the first time that SNM treatment response in male patients with impaired bladder emptying can be predicted with the BOO-contractility (Maastricht-Hannover) nomogram. Men below the 10th percentile are likely to be treatment non-responders, whereas the majority of men above the 10th percentile are responders. *Neurourol. Urodynam.* © 2016 Wiley Periodicals, Inc.

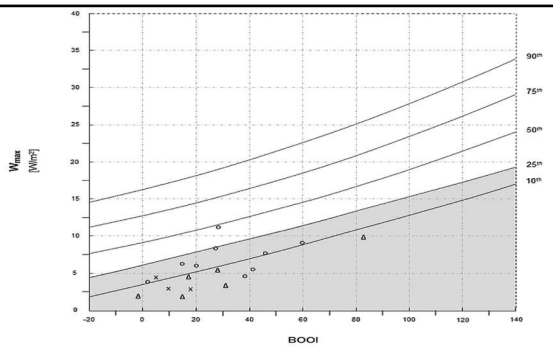


Fig. 1. Maastricht-Hannover nomogram and patients with SNM first phase implant. The figure represents patients with first phase SNM implant plotted in the BOOI-W_{max} nomogram. O (dots): represent treatment success, X (crosses): represent treatment failure, △ (triangles): represent treatment failure and complete urinary retention in medical history.

Surgical options

- Trans-urethral resection of prostate
- Intrasphincteric Botulinum Toxin
- Reduction cystoplasty
- ? Stem cells/ Tissue engineering
- Neural Reconstruction
- Detrusor Myoplasty—bladder wrap

Neural reconstruction methods of restoring bladder function

Sandra M. Gomez-Amaya, Mary F. Barbe, William C. de Groat, Justin M. Brown, Gerald F. Tuite, Jacques Corcos, Susan B. Fecho, Alan S. Braverman and Michael R. Ruggieri Sr

Gomez-Amaya, S. M. *et al. Nat. Rev. Urol.* **12**, 100–118 (2015); published online 10 February 2015; doi:10.1038/nrurol.2015.4

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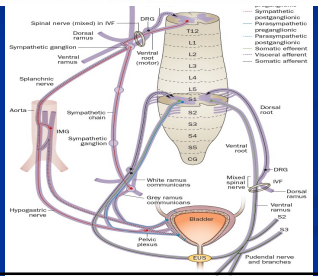
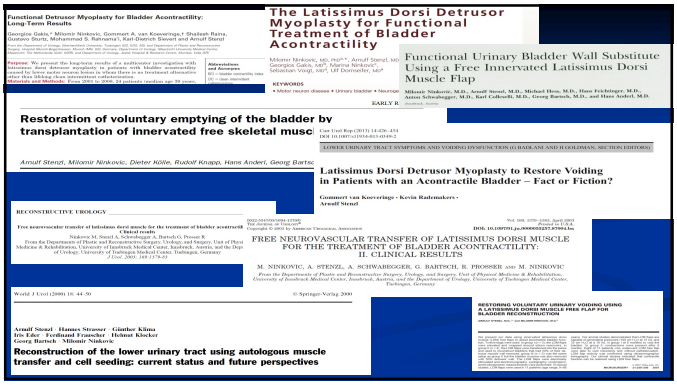




Multicenter Study: n=24

Participating Centers:

Maastricht, Netherlands
Mumbay, India
Munich Germany
Tuebingen, Germany

Functional Detrusor Myoplasty in Bladder Acontractility: Long-Term Results

Georgios Gakis,* Milomir Ninkovic, Gommert A. van Koeveringe,† Shailesh Raina, Gustavo Sturtz, Karl-Dietrich Sievert and Arnulf Stenzl

Eberhard-Karls University, Tuebingen (GG, KDS, AS), and Department of Plastic and Reconstructive Surgery, Hospital Munich-Bogenhausen, Munich (MN, GS), Germany, Department of Urology, Maastricht University Medical Centre, Maastricht, The Netherlands (GAV, MSR), and Department of Urology, Jaslok Hospital & Research Centre, Mumbai, India (SR)

0022-5347/11/1852-0001/0
THE JOURNAL OF UROLOGY®
Vol. 185, 000, February 2011
Printed in U.S.A.
DOI:10.1016/j.juro.2010.09.112

Conclusions

Complete (17/24) or partial spontaneous voiding (3/24), CR+PR 20/24 patients (83%)

91% (21/23 patients) without recurrent UTIs postoperatively

No deterioration of the upper urinary tract during F/U time period of up to 7.5 years

Fusion Biopsy: Where are we?

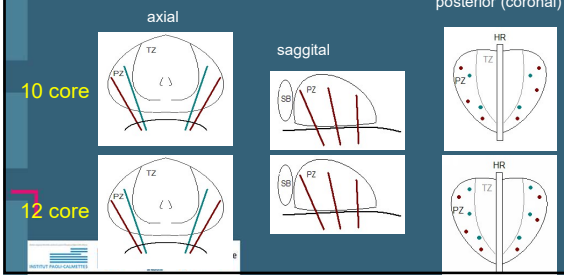
Jochen Walz
Institut Paoli-Calmettes Cancer Centre, Marseille/France

CONFEDERACION AMERICANA DE UROLOGIA/EUROPEAN ASSOCIATION OF UROLOGY/EUROPEAN SCHOOL OF UROLOGY
6º Educative Program for Residents of Confederación Americana de Urología (CAUREP)

Introduction

- „For initial diagnosis, perform a core biopsy of 10-12 systematic transrectal or transperineal peripheral zone biopsies under ultrasound guidance.“

EAU prostate cancer guidelines 2016



Introduction

Randomized multicore biopsy is standard, but associated with:

- Low diagnostic yield = 40% detection rate at 1st biopsy series

Chun et al., EurUrol 2007

- False negative rate for significant cancer is 25-35% if compared to template biopsy

Ahmed et al., Lancet 2017

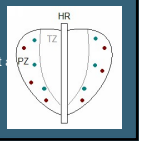
Imaging for diagnosis of prostate cancer

Suspicious region in imaging = targeted biopsy

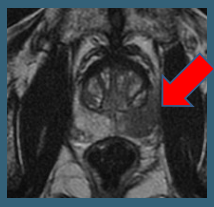
Advantage of targeted biopsies over randomized biopsies:

- Better quality = fewer cores necessary
- Better evaluation of the lesion (centered core)
- Lower costs
- Independent of chance

Pallwein et al., Eur Radiol 2007; Aigner et al.,J Urol 2010; Hoek et

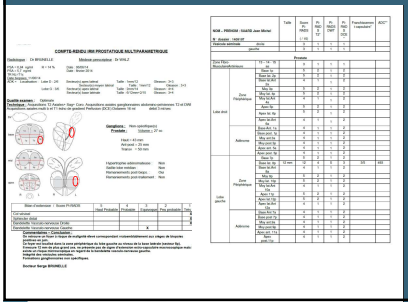


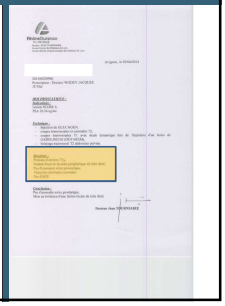
How to get the target?



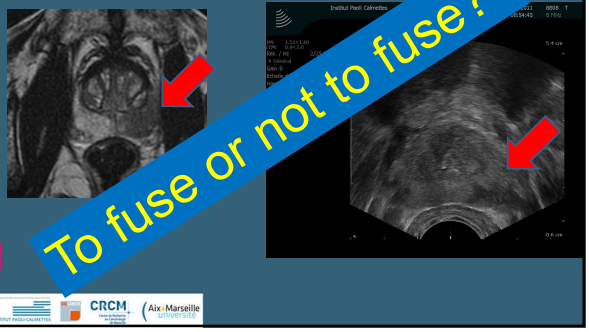
Need of standardized MRI report for reliable information transfer

Recommended standard vs. improvable





How to get the target?

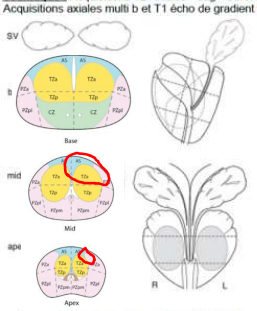


To fuse or not to fuse?

Cognitive fusion

PSA = 5,7 ng/ml Date : février 2014

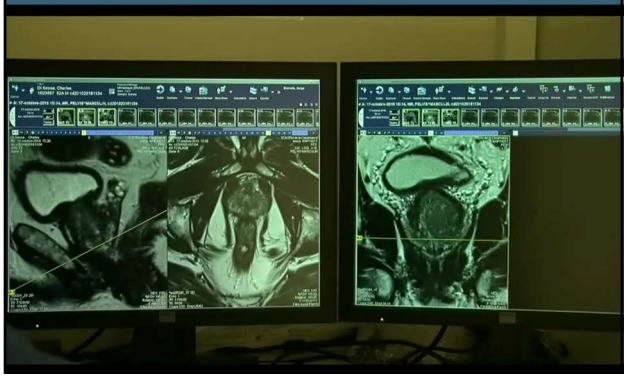
Technique : Acquisitions T2 Axiales+ Sag+ Coro. Acquisitions axiales ganglionnaires abd
Acquisitions axiales multi b et T1 écho de gradient Perfusion (DCE) Dotarem 16 ml



Ganglions : Non-spécif
Prostate : Volu
Haut = 43 mm
Ant-post = 25 m
Transv = 50 m
Hypertrophie adénomateu
Saillie lobe médian :
Remaniements post-biops
Remaniements post-traite

Bilan d'extension / Score Pi-RADS	5 Haut Probable	4 Probable

Cognitive fusion



Software fusion: 3D-navigation devices

- Electromagnetic
- Mechanical
- Image based

- (Optical)
- (Acoustic)

Software fusion: Fusion techniques

	MRI	US	MRI +US
• Rigid:			
• Elastic:			

Software fusion: organ and target recognition

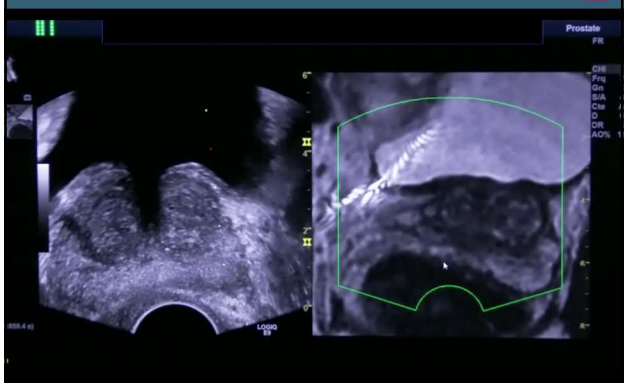
Segmentation/ Delineation:
- Manual
- Semiautomatic

Software fusion: organ and target recognition

Segmentation/ Delineation:

- Manual
- Semiautomatic
- 3D-marker based

Software fusion:

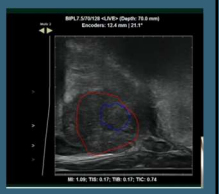


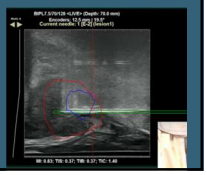
Software fusion: limitations

Software fusion prone to:

- Systematic error
  - the more steps the ↑ risk
- Misalignment
- Overestimation of capabilities

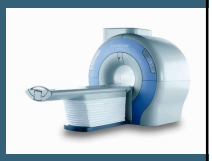
► Use your brain and knowledge!





Inbore MRI guided biopsy

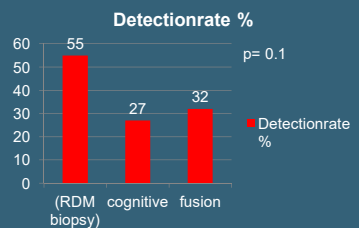
- Navigation: real time MR guided
- Needs specific material for MR environment
- Costs?
- Time?
- Resources?
- Additional randomized cores?



Beyersdorff et al., Radiology 2005

Cognitive vs. software fusion

- Head to head comparison:



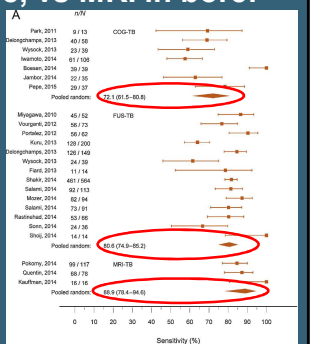
- No advantage for software fusion, except…

Wysock et al., EurUrol 2014

Meta analysis cognitive vs. software, vs MRI in bore:

Comparison detection all cancers:

- Cog vs. software: NS
- Cog vs. in bore: S
- Software vs. inbore: NS

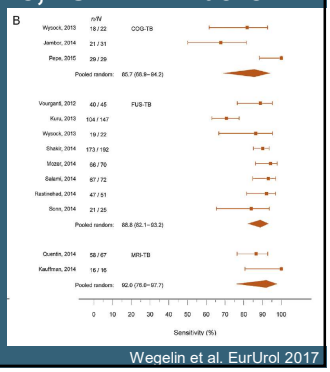


Wegelin et al. EurUrol 2017

Meta analysis cognitive vs. software, vs MRI in bore:

Comparison detection significant cancers:

- Cog vs. software: NS
- Cog vs. in bore: NS
- Software vs. inbore: NS



Wegelin et al. EurUrol 2017

Cognitive vs. software fusion

Table 8 – Multivariate analysis of positive magnetic resonance imaging–ultrasound fusion targeted biopsy and negative visually estimated targeted biopsy

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age, yr	1.01	0.96–10.7	0.704	1.05	0.98–1.14	0.181
PSA, ng/ml	0.96	0.85–1.08	0.509	0.91	0.78–1.08	0.280
Prostate volume, MRI, ml	0.99	0.96–1.00	0.168	0.98	0.96–1.00	0.187
mSR suspicion score:						
2	Ref	–	–	Ref	–	–
3	0.83	0.25–2.71	0.756	1.55	0.39–6.10	0.534
4	0.84	0.24–2.99	0.786	1.45	0.32–6.55	0.630
5	0.75	0.15–3.84	0.73	0.64	0.06–7.11	0.715
mSR diameter	0.89	0.80–1.00	0.048	0.83	0.73–0.95	0.005
mSR maximal area	1.15	0.66–2.00	0.631	2.27	0.81–6.38	0.120
mSR location						
Posterior	Ref	–	–	Ref	–	–
Anterior	2.99	1.07–8.33	0.037	3.84	1.00–14.72	0.050
Operator experience with VE-TB						
Inexperienced	Ref	–	–	Ref	–	–
Experienced	0.76	0.29–.197	0.572	0.64	0.19–2.13	0.467

OR = odds ratio; CI = confidence interval; PSA = prostate-specific antigen, MRI = magnetic resonance imaging; mSR = magnetic resonance imaging–suspicious regions; VE-TB = visually estimated targeted biopsy.

Wysock et al., EurUrol 2014

When is software fusion especially helpful?

- Anterior lesion
- Small lesion (no cut-off available)

Wysock et al., EurUrol 2014

- When limited information transfer from radiology to urology
- When limited experience with MRI and/or US
- When pathway should be “foolproof”
- When need of documentation

How many cores do we need to take?

- XXXX

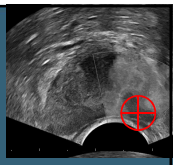
How many cores do we need to take?

- XXXX

How many cores do we need to take?

- XXXX

Imaging for diagnosis of prostate cancer



Suspicious region in imaging = targeted biopsy

Advantage of targeted biopsies over randomized biopsies:

- Better quality = fewer cores necessary
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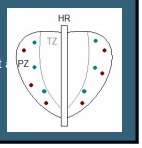
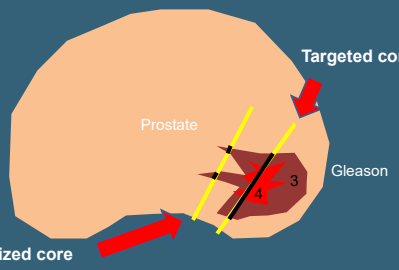
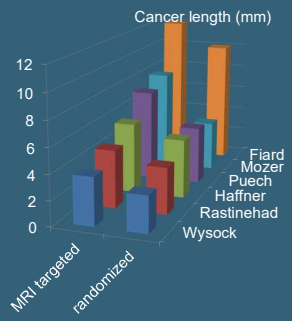
Pallwein et al., Eur Radiol 2007; Aigner et al.,J Urol 2010; Hoek et a



Cancer significance: Targeted vs. randomized biopsy

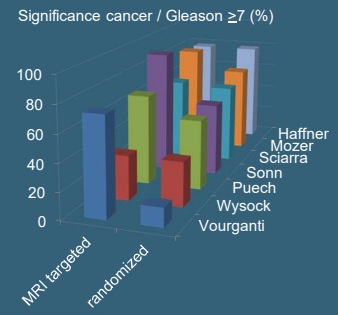


MRI targeted vs. randomized: Cancer length:



Van Hove et al., WJU 2014

MRI targeted vs. randomized: Significance of cancer



Van Hove et al., WJU 2014

Risk assessment in active surveillance

- Reclassification after MRI guided biopsy in 20-36% of cases

Hu et al. J Urol 2014; Walton et al., Urol Oncol 2015

- MRI targeted biopsy increases the likelihood of correctly sample and grade the lesion

Baco et al. EurUrol 2015, Lanz et al. J Urol 2016

►Major achievement for the safety in active surveillance

Recommendations in men on active surveillance	LE	Strength rating
Perform multiparametric magnetic resonance imaging before a confirmatory prostate biopsy, if not done before the first biopsy.	1a	Strong
Perform the combination of targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy at confirmatory biopsy.	2a	Weak

EAU prostate cancer guidelines 2019

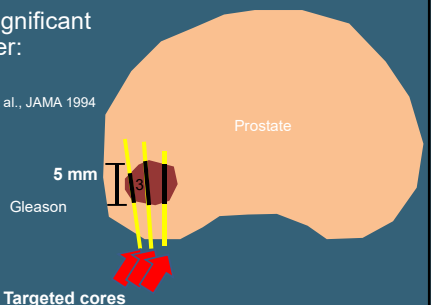
Problem of targeted biopsy vs randomized biopsy

Definition of significant prostate cancer:

- ≤ 2 cores +

Epstein et al., JAMA 1994

- One core +

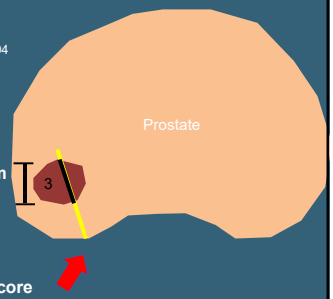


Problem of targeted biopsy vs randomized biopsy

Definition of significant prostate cancer:

- <50% of core involved
  Epstein et al., JAMA 1994
- < 3mm cancer per core

5 mm diameter:
(0.5 x 0.5 x 0.5) x 0.52= 0.06cc



Meta analysis targeted vs. randomized Biopsy: Conclusion (?)

"The heterogeneous usage of definitions for csPCa ...is a major concern for this current meta-analysis ... because most definitions have their origin in the systematic biopsy setting. ...they are.... based on....cancer core length, and number of positive cores and therefore might significantly overestimate the number of detected csPCa in a targeted biopsy setting."

Wegelin et al. EurUrol 2017

Conclusions I

- In order to improve the diagnostic work up of prostate cancer standardization, training, respect of recommendations and quality assurance are key
- Cognitive fusion seems to be comparable to software fusion in experienced hands
- Software fusion of interest for small and/or anterior lesions

Conclusions II

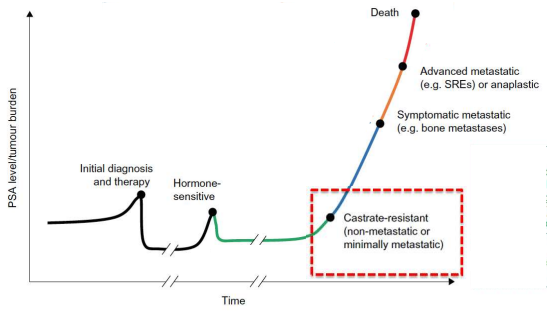
- Targeted biopsies give more precise information about true grade and size
- Statements regarding "significance" of detected cancers depend on definition

Castration resistant prostate cancer Update

FRANCISCO RODRIGUEZ-COVARRUBIAS

Department of Urology
Instituto Nacional de Ciencias Médica y Nutrición Salvador Zubirán
Mexico City

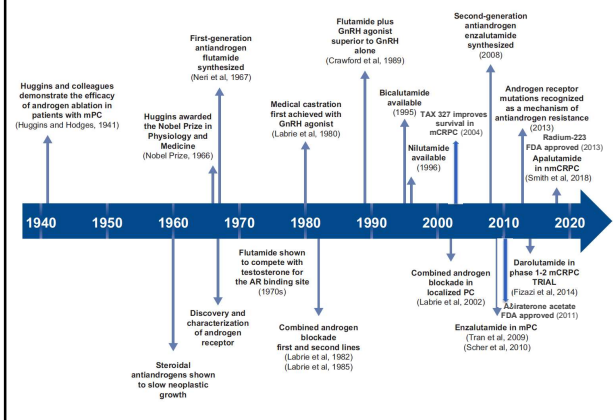
Prostate cancer natural history



Disclosure

Speaker for Bayer, Ferring, GSK, Janssen, Lilly-Icos y MSD

CRPC Landscape



Modified from Crawford ED et al. J Urol 2018; 200(5):956-966

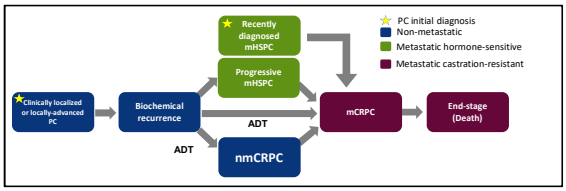
CRPC - ¿Stages?

Possible clinical scenarios:

- Asymptomatic / minimally symptomatic nmCRPC (M0)
- Asymptomatic / minimally symptomatic mCRPC, CT-naïve
- Symptomatic mCRPC, good performance status, CT-naïve
- Symptomatic mCRPC, poor performance status, CT-naïve
- Symptomatic mCRPC, good performance status, previous CT
- Symptomatic mCRPC, poor performance status, previous CT

Lowrance WT et al. CRPC AUA Guideline Amendment 2018. J Urol 2018; In Press

Landscape



PC, prostate cancer;
ADT, androgen deprivation therapy;
mHSPC, metastatic hormone-sensitive PC;
nmCRPC, non-metastatic castration-resistant prostate cancer;
mCRPC, metastatic castration-resistant prostate cancer

Adapted from: Scher HI, et al. J Clin Oncol. 2016;34:1402-18. Mottet N, et al. EAU/ESTRO/ESUR/SIOG Guidelines on Prostate Cancer 2017. Available from: http://uroweb.org/guideline/prostate-cancer. Accessed February 2018. Hong JH, Kim IY. Korean J Urol. 2014;55:153-60.

CRPC – Imaging

M0 Castrate-Res Patients

1st conventional scan PSA level ≥2 ng/ml

Imaging frequency if n for previous conventio

2nd conventional scan PSA=5 ng/ml and every doubling of PSA level t (based on PSA testing 3 months)

M1 Castrate-Re Patients*

Utilize conventional sca consider NGI only if con scans are negative and clinican still suspects di progression

Crawford ED et al. J Urol 2018; In Press

CRPC – Definitions

- Serum Testosterone ≤ 50 ng/dL ó 1.7 nmol/L
- Three consecutive PSA raises one week apart resulting in two 50% increases over the nadir
- A.P.E. > 2 ng/mL

Non-Metastatic	Metastatic
Negative bone scan Negative CT scan	Radiological progression (RECIST) • Two or more new bone lesions (Bone scan) • Soft tissue lesion

EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2018

nmCRPC – Imaging

RADAR III Recommendations

- Initial evaluation: PSA ≥ 2 ng / mL
- Imaging frequency if initial work-up was negative:
  - Second evaluation when PSA = 5 ng / mL and every time PSA doubles (every three months)

Crawford ED et al. J Urol 2018; In Press

CRPC - Evaluation

New generation imaging

Radiotracer	Action/ Target	Indications	Pros	Cons
^{18}F-FACBC (fluciclovine)	Amino acid transport	Detection of local and distant recurrence	Slow urinary excretion improving signal; more sensitive at lower PSA levels than acetate and choline	Moderate specificity and moderate performance at low PSA cut-offs
^{11}C-choline	Cell membrane synthesis	Detection of recurrent disease in lymph node and soft tissues	Minimal bladder excretion	Short half-life; variable sensitivity and specificity for BCR particularly at low PSA cut-offs; availability of cyclotron
^{68}Ga-PSMA	Targets PSMA	High detection rate of local and distant sites of recurrence, also of metastatic disease in high-risk patients undergoing primary definitive therapy	High detection rates even at low PSA levels	Requirement of a ^{68}Ga generator
^{18}F-DCFBC	Targets PSMA	For better selection of primary definitive therapy, both hormone-sensitive and CRPC	Longer half-life than ^{68}Ga	First generation of ^{18}F-labeled urea; considerable blood pool activity, being investigated in clinical trials
^{18}F-DCFPyL	Binds PSMA	Detection of occult lymph nodes before primary definitive treatment, early local and distant recurrence	More sensitive to detect occult lymph nodes before primary definition therapy; higher tumor to background ratios due to high affinity	Still being investigated in phase 3 clinical study
^{11}C-acetate	Lipid synthesis	Identification of metastatic disease	Ability to image both soft tissue and skeletal mets; minimal bladder excretion	Short half-life; availability of cyclotron

CRPC –Imaging

RECIST criteria

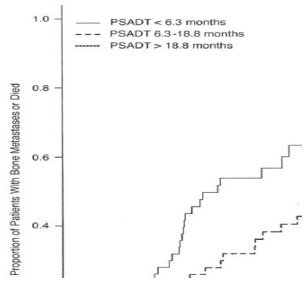
4.3.1. *Evaluation of target lesions*

Complete Response (CR): Disappearance
Any pathological lymph nodes
non-target) must have reducti
<10 mm.

Progressive Disease (PD): At least a 20%
of diameters of target lesions,
the *smallest sum on study* (this i
sum if that is the smallest on s
the relative increase of 20%, the
onstrate an absolute increase of
the appearance of one or more

Eisenhauer EA et al. Eur J Cancer 2009; 45(2):228-247

PSA-DT and metastases free survival



PSA-DT (< 6.3, 6.3 a 18.8, > 18.8 meses) impacts bone metastases free survival (p < 0.001)

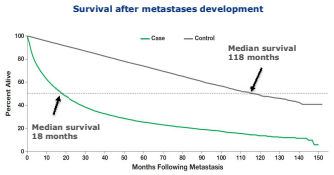
Smith MR, et al. J Clin Oncol. 2013;31:3800-3806.

CRPC –Risk factors for progression

- Advanced age
- Time from diagnosis
- PSA levels
- Short PSA-DT

Moreira DM et al. Clin Genitourin Cancer 2017; 15: 60

Impact of bone metastases on survival



- **Metastases were associated with higher mortality**
  - **HR= 4.79**
  - **95% CI: 4.63-4.96**
  - **p < 0.0001**

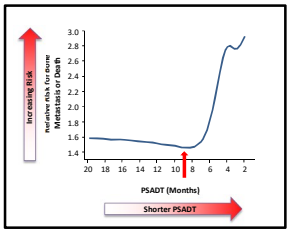
- Metastatic progression in patients with PCa and loco-regional disease are at higher risk of PCa related mortality

Li T, et al. ASCO-GU 2016. Abstract (and poster) E10

PSA-DT predicts bone metastases or death

CRPC patients with PSA-DT <10 months have higher risk for progression or PCa related death

Example of PSA-DT calculator:
https://www.mskcc.org/nomograms/prostate/psa_doubling_time



Smith MR, et al. J Clin Oncol. 2013;31:3800-3806.

Benefits of delaying metastases

Reduction in:[1-3]

Symptomatic progresión	Morbidity	Mortality	Use of health resources

- Metastatic disease is a critical stege in CRPC[1-3]
- Thus, delaying metastatic progression should be one of our goals.[4]

1. Luo, et al. Oncology (Williston Park). 2016 Apr;30(4):336-44; 2. Li TT et al. Cancer. 2017;123(18):3591-3601; 3. Li T, et al. ASCO-GU 2016. Abstract (and poster) E10; 4. Tombal B. Ann Oncol. 2012 Sep;23 Suppl 10:x251-8

nmCRPC M0 – Treatment options

The NEW ENGLAND JOURNAL of ME
March 18, 2019

ORIGINAL ARTICLE

Darolutamide in Nonme
Castration-Resistant Prosta

The NEW ENGLAND JOURNAL of M
April 12, 2018

ORIGINAL ARTICLE

Apalutamide Treatment and M
Survival in Prostate C

Matthew R. Smith, M.D., Ph.D., Fred S
Simon Chowdhury, M.B., B.S., Ph.D., Stéphane C

	SPARTAN[6]	PROSPER[7]	ARAMIS[22]
Number of patients	• 1,207	• 1,401	• 1,509
Treatment arms	• Apalutamide + ADT (n=806) • Placebo + ADT (n=401)	• Enzalutamide + ADT (n=933) • Placebo + ADT (n=468)	• Darolutamide + ADT (n=955) • Placebo + ADT (n=554)
Inclusion criteria	• nmCRPC N0/N1 • PSADT ≤10 months	• nmCRPC N0 • PSADT ≤10 months	• nmCRPC • PSADT ≤10 months
Median follow-up at time of primary analysis	• 20.3 months	• 18.5 months in the enzalutamide arm, 15.1 months in the placebo arm	• 17.9 months
MFS (primary endpoint)	• Apalutamide: 40.5 months • Placebo: 16.2 months	• Enzalutamide: 36.6 months • Placebo: 14.7 month	• Darolutamide: 40.4 months • Placebo: 18.4 months
HR (95% CI), p-value	• 0.28 (0.23–0.35), p<0.0001	• 0.29 (0.24–0.35), p<0.001	• 0.41 (0.34–0.50), p<0.0001
OS (secondary endpoint)	• Median not reached in apalutamide arm; 39 months in placebo arm. • 30% reduction in ACM with apalutamide (HR: 0.70, p=0.07).	• Median not reached in either treatment arm. • 20% reduction in ACM with enzalutamide (HR: 0.80, p=0.1519).	• Median not reached in either treatment arm. • 29% reduction in ACM with darolutamide (HR: 0.71, p=0.1519).

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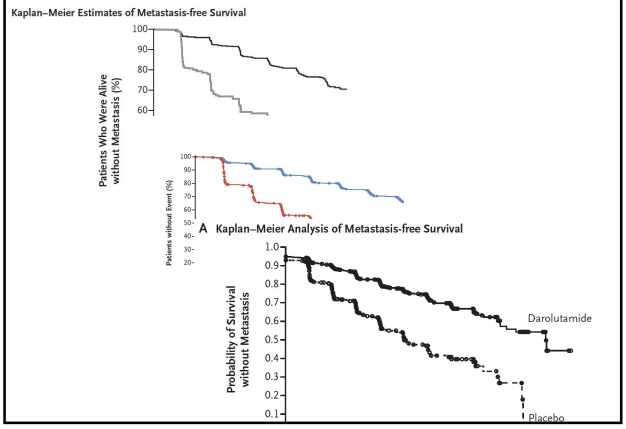
JOURNAL of MED
ESTABLISHED IN 1812 JUNE 28, 2018

Enzalutamide in Men with Nonmetastatic,



	Apalutamide+ADT (SPARTAN; N=803)[4]	Enzalutamide (PROSPER; N=930)[7]	Darolutamide (ARAMIS; N=954)[29]
Any adverse event	775 (96.5)	808 (86.9)	794 (83.2)
Any serious adverse event	199 (24.8)	226 (24.3)	237 (24.8)
Adverse event leading to discontinuation of the trial regimen	85 (10.6)	87 (9.4)	85 (8.9)
Most common adverse events (all grades), occurring in >10% of patients in any group			
Fatigue	244 (30.4)	303 (32.5)	115 (12.1)
Hypertension	199 (24.8)	111 (11.9)	63 (6.6)
Rash	191 (23.8)	NR	NR
Diarrhoea	163 (20.3)	91 (9.8)	66 (6.9)
Nausea	145 (18.1)	106 (11.4)	48 (5.0)
Weight loss	129 (16.1)	55 (5.9)	34 (3.6)
Arthralgia	128 (15.9)	78 (8.4)	77 (8.1)
Falls	125 (15.6)	106 (11.4)	40 (4.2)
Fracture	94 (11.7)	NR	40 (4.2)
Hot flush	NR	121 (13.0)	50 (5.2)
Deaths	10 (1.2)	32 (3.4)	37 (3.9)

nmCPRC – Optimal management

- Three new generation antiandrogens have demonstrated improvement in Metastases-free survival
- Overall Survival results still “immature”
- However, metastases related morbidity has decreased

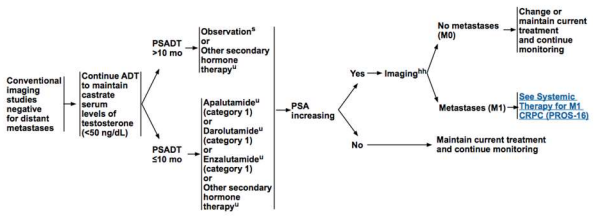
Higano C. Nature Reviews 2019; 16: 335-336

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR M0 CASTRATION–RESISTANT PROSTATE CANCER (CRPC)



CRPC M1 – Treatment options

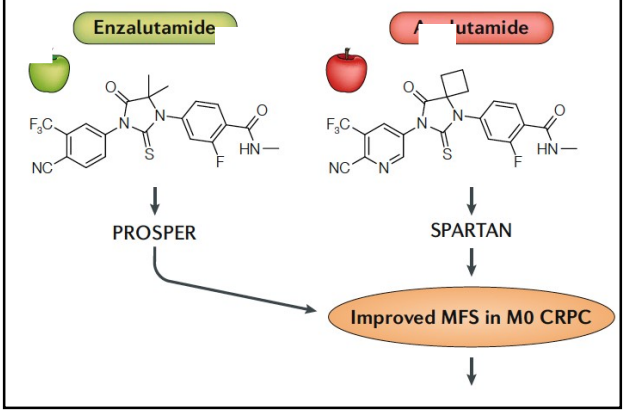


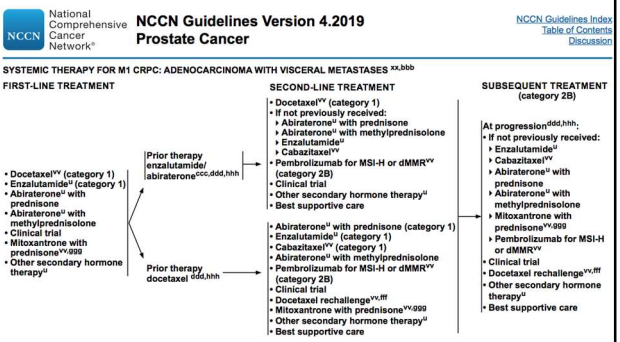
Table 1. *FDA approved anticancer treatments for mCRPC, excluding treatments specifica*

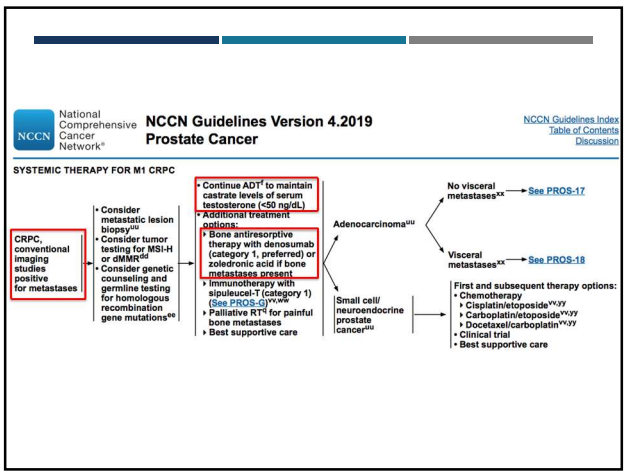
Treatment	Mechanism	Indication	
Docetaxel (Taxotere®)*	Taxane chemotherapy (microtubule inhibitor)	mCRPC	75
Sipuleucel-T (Provenge®)	Autologous cellular immunotherapy	Asymptomatic or minimally symptomatic mCRPC	25
Cabazitaxel (Jevtana®)*	Taxane chemotherapy (microtubule inhibitor)	mCRPC with previous docetaxel treatment	25
Abiraterone acetate (Zytiga®)*	CYP17 (androgen synthesis)	mCRPC	10

Crawford ED et al. J Urol 2015; 194:1537-1547

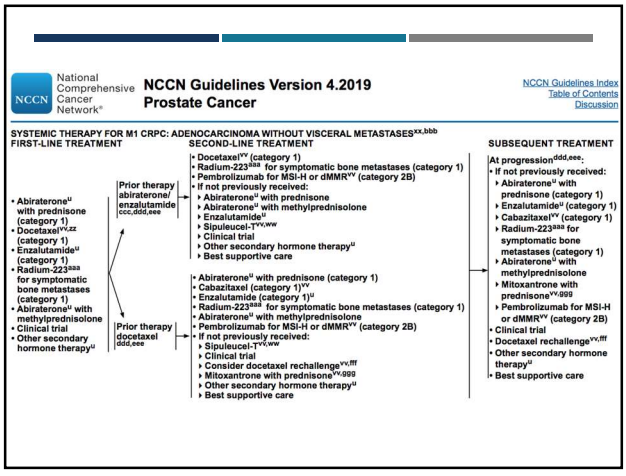
Table 2 | **Second-line and third-line therapies with a survival advantage in metastatic cast**

Study	Mechanism of action	Study arms
Abiraterone		
COU-AA-302 (REFS[184,185]) (before chemotherapy)	Hormone therapy: inhibits CYP17 enzyme	Abiraterone + prednisone versus placebo + prednisone
COU-AA-301 (REF.[198]) (after chemotherapy)	Hormone therapy: inhibits CYP17 enzyme	Abiraterone + prednisone versus placebo + prednisone
Enzalutamide		
TERRAIN[182]	Hormone therapy: inhibits binding of androgen to the receptor	Enzalutamide + ADT versus bicalutamide + ADT
STRIVE[199]	Hormone therapy: inhibits binding of androgen to the receptor	Enzalutamide + ADT versus bicalutamide + ADT
PREVAIL[181] (before chemotherapy)	Hormone therapy: inhibits binding of androgen to the receptor	Enzalutamide versus placebo





CRPC – Multidisciplinary approach



CRPC – Optimal management

Idealy:

- Medical team integrated by urologists, medical oncologists, radiation oncologists, nuclear medicine specialists, geriatricians, oncology nurse
- All members should be trained looking for patient well being
- Multidisciplinary approach will be useful to improve therapeutic strategies

Sartor AO and Fitzpatrick JM. BJU Int 2012; 110 (3): 328-335

Conclusions

- Eventually, all patients with advanced Prostate Cancer will develop CRPC
- Delaying metastases could reduce morbidity and mortality
- Multidisciplinary management is relevant for patient benefit
- Accurate identification of factors of progression will allow better use of therapeutic alternatives
- Increasing availability of new agents poses a challenge in terms of proper selection, sequence and use

Clinical implications on daily practice of MRI of the prostate

Jochen Walz
Institut Paoli-Calmettes Cancer Centre, Marseille/France

CONFEDERACION AMERICANA DE UROLOGIA/EUROPEAN ASSOCIATION OF UROLOGY/EUROPEAN SCHOOL OF UROLOGY
6º Educative Program for Residents of Confederación Americana de Urología (CAUREP)

Prostate cancer diagnosis

Randomized multicore biopsy used to be standard, but associated with:

- Low diagnostic yield = 40% detection rate at 1st biopsy series

Chun et al., EurUrol 2007

- False negative rate for significant cancer is 25-35% if compared to template biopsy

Ahmed et al., Lancet 2017

►Need to become better

► Use MRI ?

What are clinical implications of MRI guided biopsies?

- Detection rates

► Comparison to 10-12 core biopsy

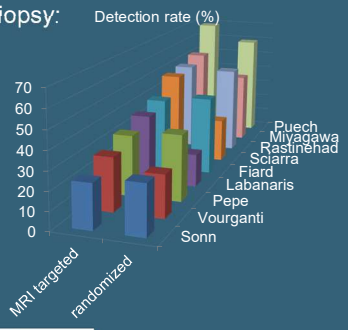
MRI targeted vs. randomized

Initial biopsy:
Significant cancers

modified from: Schoots et al., EurUrol 2015; van Hove et al., WJU 2014

MRI targeted vs. randomized: Detection rates

Repeat biopsy:



Van Hove et al., WJU 2014

Clinical implications for MRI guided biopsy

- EAU Guidelines:

Recommendations in biopsy-naïve patients	LE	Strength rating
Perform mpMRI before prostate biopsy.	1a	Weak
When mpMRI is positive (i.e. PI-RADS ≥ 3), combine targeted and systematic biopsy.	2a	Strong
When mpMRI is negative (i.e. PI-RADS ≤ 2), and clinical suspicion of prostate cancer is low, omit biopsy based on shared decision making with the patient.	2a	Weak

EAU prostate cancer guidelines 2019

Clinical implications for MRI guided biopsy

- EAU Guidelines:

Recommendations in patients with prior negative biopsy	LE	Strength rating
Perform mpMRI before prostate biopsy.	1a	Strong
When mpMRI is positive (i.e. PI-RADS ≥ 3), perform targeted biopsy only.	2a	Weak
When mpMRI is negative (i.e. PI-RADS ≤ 2), and clinical suspicion of prostate cancer is high, perform systematic biopsy based on shared decision making with the patient.	2a	Strong

EAU prostate cancer guidelines 2019

- AUA /SAR consensus: "When high quality prostate magnetic resonance imaging is available, it should be strongly considered for any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer. ...

Rosenkrantz et al. J Urol 2016

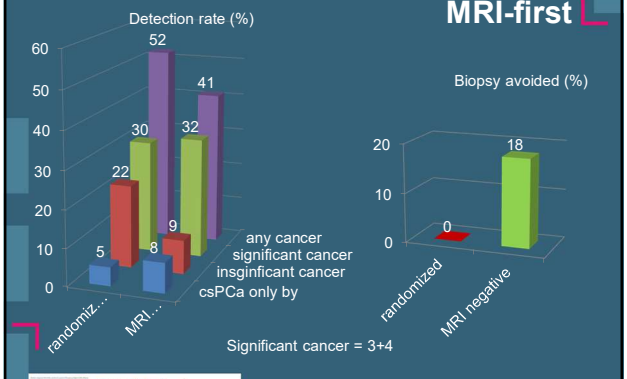
MRI-first

- n= 251 patients

Biopsy naïve man
↓
Mutliparameric MRI
↓
Randomized biopsy (12 cores) + 2 cores on US-lesion
↓
MRI targeted biopsy max 2 lesions/3 cores
↓
Signifcant Prostate cancer (GG ≥2) detection rate

Rouvriere et al., Lancet Oncol 2018

MRI-first



Rouvriere et al., Lancet Oncol 2018

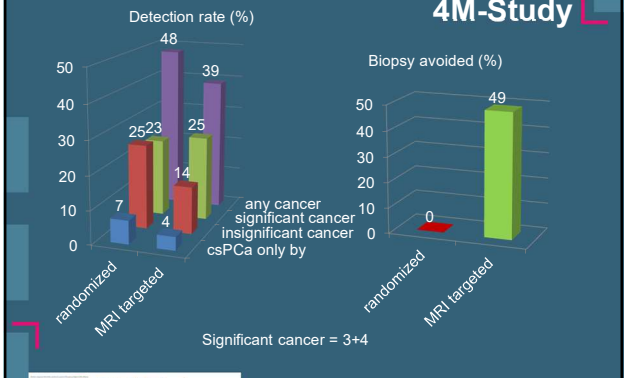
4M-Study

- n= 626 patients

Biopsy naïve man
↓
Mutliparameric MRI (3T)
↓
MRI in-bore targeted biopsy of all PI-RDAS3-5 lesions/ 2-4 cores
↓
Randomized biopsy (12 cores) including US-lesion
↓
Significant prostate cancer (GG ≥2) detection rate

van der Leest et al., EurUrol 2018

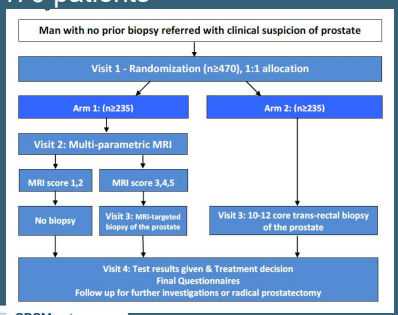
4M-Study



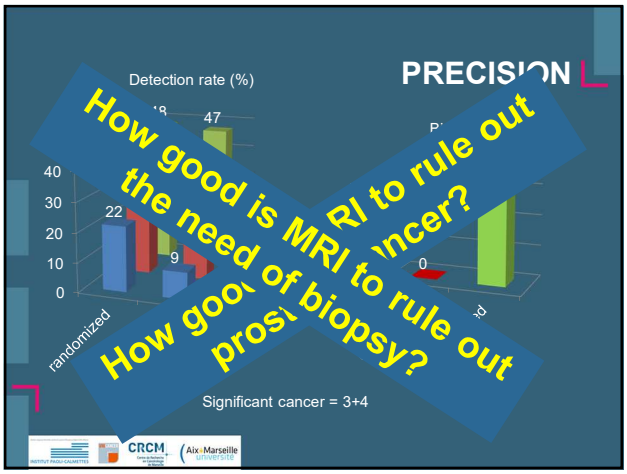
van der Leest et al., EurUrol 2018

PRECISION

- n= 470 patients



Kasivisvanathan et al., NEJM 2018



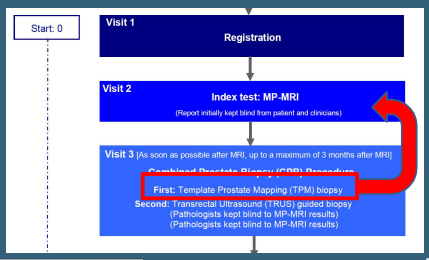
How about MRI to rule out significant prostate cancer?

- How about the NPV of mpMRI?
- If NPV is high, a negative mpMRI may be a tool for ruling out significant disease =
  - Tool for triage before 1st biopsy
  - Tool for triage before repeat biopsy
  - Tool for active surveillance

Vargas et al., Radiology 2011
Rastinehad et al., J Urol 2011.
Villers et al., J Urol 2006
Ahmed et al., Nat Rev Clin Oncol 2009
Haffner et al., BJUI, 2011
Ahmed et al. Lancet 2017

PROMIS

- N=576 patients



Ahmed et al., Lancet 2017

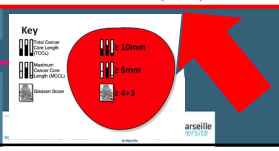
PROMIS: What do we learn? Results depend very much on definitions

	MP-MRI, % (95% CI)	TRUS-biopsy, % [95% CI]	Test ratio* [95% CI]	p value
Primary definition (Gleason score ≥4+3 or cancer core length ≥6 mm), prevalence of clinically significant cancer 230 (40%, 36–44%)				
Sensitivity test	93 (88–96)	48 (42–55)	0·52 (0·45–0·60)	p<0·0001
Specificity test	41 (36–46)	96 (94–98)	2·34 (2·08–2·68)	p<0·0001
PPV	51 (46–56)	90 (83–94)	8·2 (4·7–14·3)	p<0·0001
NPV	89 (83–94)	74 (69–78)	0·34 (0·21–0·55)	p<0·0001
Secondary definition (Gleason score ≥3+4 or cancer core length ≥4 mm), prevalence of clinically significant cancer 331 (57%, 53–62%)				
Sensitivity test	87 (83–90)	60 (55–65)	0·69 (0·64–0·76)	p<0·0001
Specificity test	47 (40–53)	98 (96–100)	2·11 (1·85–2·41)	p<0·0001
PPV	69 (64–73)	98 (95–100)	22·7 (8·6–59·9)	p<0·0001
NPV	72 (65–79)	65 (60–70)	0·70 (0·52–0·96)	p=0·025
Any Gleason score 7 (≥3+4), prevalence of clinically significant cancer 308 (53%, 49–58%)				
Sensitivity test	88 (84–91)	48 (43–54)	0·55 (0·49–0·62)	p<0·0001
Specificity test	45 (39–51)	99 (97–100)	2·22 (1·94–2·53)	p<0·0001
PPV	65 (60–69)	99 (95–100)	40·8 (10·2–162·8)	p<0·0001
NPV	76 (69–82)	63 (58–67)	0·53 (0·38–0·73)	p<0·0001

Ahmed et al., Lancet 2017

Influence of definitions on NPV

	MP-MRI, % (95% CI)	TRUS-biopsy, % [95% CI]	Test ratio* [95% CI]	p value
Primary definition (Gleason score ≥4+3 or cancer core length ≥6 mm), prevalence of clinically significant cancer 230 (40%, 36–44%)				
Sensitivity test	93 (88–96)	48 (42–55)	0·52 (0·45–0·60)	p<0·0001
Specificity test	41 (36–46)	96 (94–98)	2·34 (2·08–2·68)	p<0·0001
PPV	51 (46–56)	90 (83–94)	8·2 (4·7–14·3)	p<0·0001
NPV	89 (83–94)	74 (69–78)	0·34 (0·21–0·55)	p<0·0001



Ahmed et al., Lancet 2017

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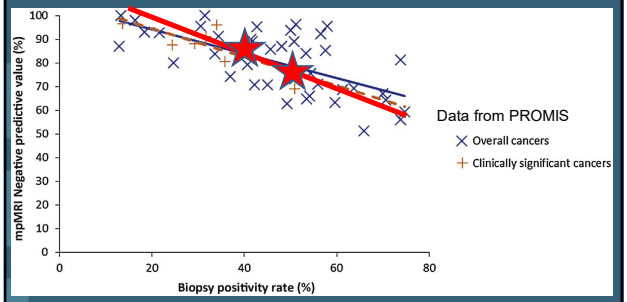
Ahmed et al., Lancet 2017

Prevalence and NPV



Moldovan et al. EurUrol 2017

Pivotal aspects of PROMIS

- Systematic quality assurance protocol

Consequences:

- "Scans deemed of insufficient quality repeated before biopsy"

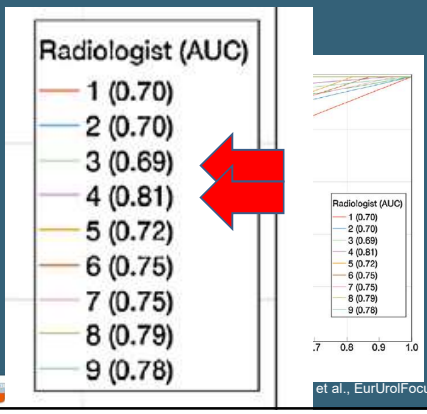
Ahmed et al., Lancet 2017

- 11 centres participated
- 3-5 possible centers excluded, because of insufficient quality

Personal communication by Hashim Ahmed + Marc Emberton, 2017

- Some centres unable to provide sufficient quality despite expert training and expert support for set-up

Variability of reader performance



et al., EurUrolFocus 2018

Influence of expertise on MRI performance

Prostate cancer detection (ROC):

- General Radiologist: 0.66
- Uro-Radiologist: 0.88

Scheidler et al., ROFO 2012

- Before training: 0.74
- After training: 0.88

Garcia-Reyes et al., Abdom Imaging 2015

Influence of expertise on MRI performance

Characteristics of missed prostate cancers	General mpMRI	Expert mpMRI	p=
Pathological stage T3	22%	3%	0.02
Primary pGleason 4	18%	3%	0.05
Global tumor volume (mL)	1.10	0.67	0.05

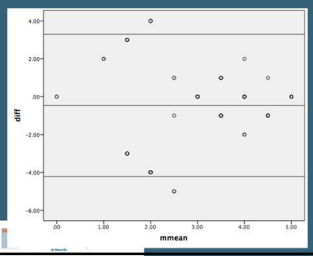
Branger et al., BJUI 2016

Variability of interpretation + PI-RADS score

N= 126 patients with repeat MRI due to referral

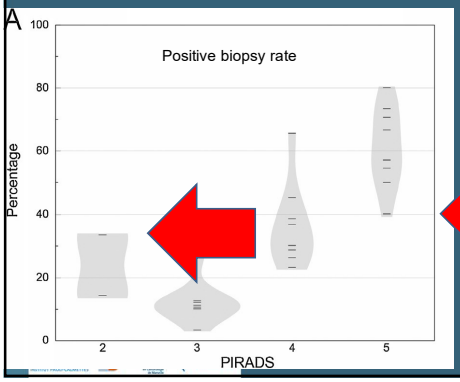
►very poor level of agreement

►significant difference in PI-RADS score



Müller et al.; WJU 2018

Variability of PI-RADS score



Sonn et al., EurUrolFocus 2018

How good is MRI to rule out prostate cancer?

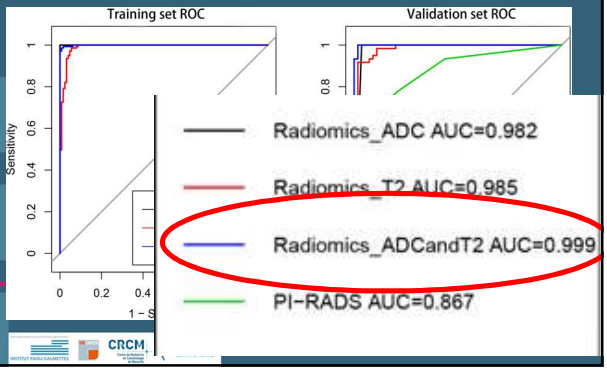
- Performance depends on where the MRI is done
- Performance depends on who reads and reports the MRI

Perspectives?

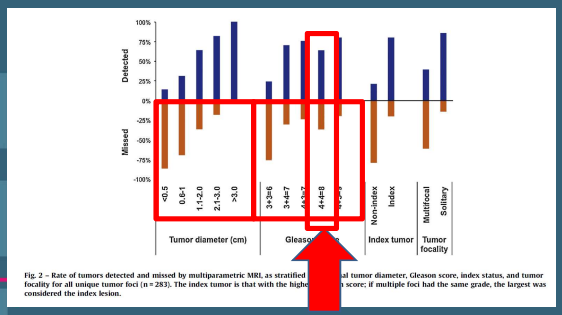
Radiomics and artificial intelligence are prone to overcome these problems:

- Center dependency
- Operator/Reader dependency

Prostate cancer diagnosis



Prostate cancer missed by mpMRI



Le et al.; EurUrol 2015

Prostate cancer missed by mpMRI

Table 3

Gleason score	
3+3	0 (0)
3+4	17 (65) **=20% of all 3+4**
4+3	1 (4)
4+4	7 (27) **=14% of all 4+4**
4+5	1 (4)

Borofsky et al., Radiology 2018

Cribriform prostate cancer missed by mpMRI

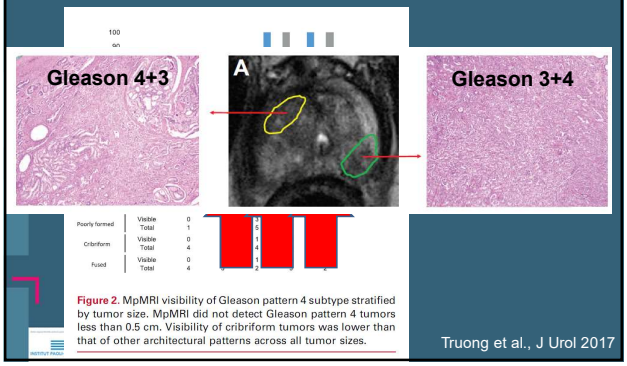
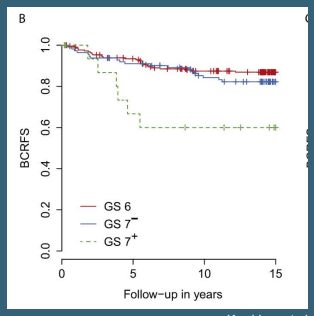


Figure 2. MpMRI visibility of Gleason pattern 4 subtype stratified by tumor size. MpMRI did not detect Gleason pattern 4 tumors less than 0.5 cm. Visibility of cribriform tumors was lower than that of other architectural patterns across all tumor sizes.

Truong et al., J Urol 2017

Outcome cribriform PCa



Kweldam et al., Eur J Cancer 2016

How good is MRI to rule out prostate cancer?

- Performance depends on cancer characteristics and histology

Perspectives?

Radiomics and artificial intelligence are prone to overcome these problems:

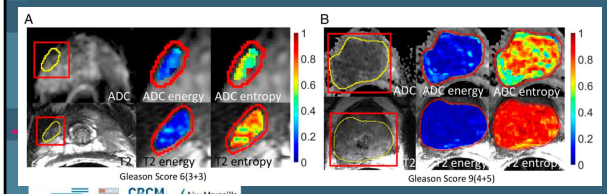
- Unreliable Grading
- Unreliable Staging

►better decision making

Grading

Performance of ADC-T2w-texture features:
Differentiation between:

- 3+3 vs.≥3+4 : AUC 0.93
- 3+4 vs. 4+3: AUC 0.92

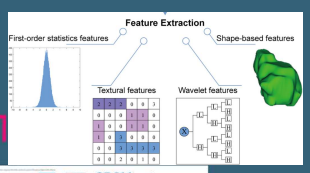


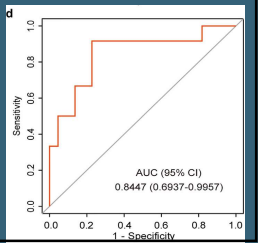
Fehr et al., PNAS 2015

Staging?

Lymph nodes invasion (bladder cancer)

- T2w MRI images
- first-order statistics features; shape-based features; statisticsbased textural features; wavelet features
- N0 vs. N1: AUC 0.85



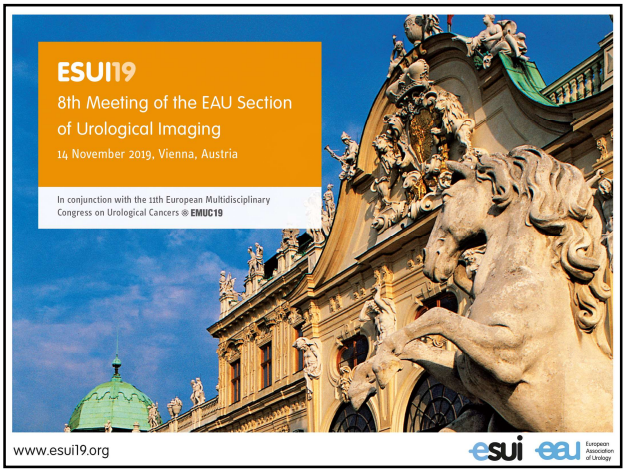


Does MRI in daily practice work?

It could if:

- You do not expect to find every [millimetre of] significant disease
- You accept that results depend on your definition of clinical significance
- You quality assure every scanner, optimize the sequences iteratively, quality control scans and have robust training for radiologists
- All centres ... evaluate their own data to determine where their own negative predictive value sits and then strive to improve upon this through a constant iterative dialogue between urology and radiology

H. Ahmed, editorial BJUI 2016



INDICATIONS AND LIMITS OF THE LAPAROSCOPIC RADICAL NEPHRECTOMY

Fundació Puigvert

Dr. J Palou
Chairman of Urology
Fundació Puigvert
Professor of Urology
Universitat Autònoma de Barcelona
Barcelona

History

Year	Author	Treatment
1991	Clayman	Laparoscopic Nephrectomy for oncocytoma
1992	Mc Dougall ONO	Transperitoneal Laparoscopic Radical Nephrectomy for renal carcinoma
1992	Coptcoat Rassweiler	Laparoscopic Radical Nephrectomy European experience
1992	Gaur	Retroperitoneoscopy
1999	Abbou Gill	Radical Nephrectomy. Retroperitoneoscopy
2000	Fundació Puigvert	1st Laparoscopic Radical Nephrectomy

fundació puigvert

Advantages of Laparoscopic Nephrectomy

- Less surgical agression
- Less blood loss
- Less analgesia
- Less hospital stay
- Long term oncologic follow up

Saika et al Urology 62:1018, 2003

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Laparoscopic renal surgery. Points of controversy

- Approach: Transperitoneal vs retroperitoneal
- Tumoral size: T1-T2-T3-T4?
- Locally advanced disease. T3b T3c N1-N2
- Cytoreductive surgery in patients with metastasis of renal carcinoma
- Laparoscopy in aged and obese patients
- Percentage of complications. Minimize the potential tumoral dissemination?

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APPROACHES	ADVANTAGES	DISADVANTAGES
Transperitoneal	• Better surgical space • Better orientation	• Difficulty in cases with previous surgeries • Higher incidence of intestinal injuries • Higher probability of ileus
Retroperitoneal	• More direct access to renal vessels • Less incidence of intestinal injuries • Applicable in cases with previous abdominal surgery	• Surgical space more limited • Difficulty in perirenal fibrosis

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Approach

Randomized prospective study regarding different laparoscopic approaches: transperitoneal (TP) vs retroperitoneal (RP)

	TP	RP
Control time of the renal artery (min.)	**91**	**34**
Control time of the renal vain (min.)	**98**	**45**
Total surgery time (min.)	**207**	**150**
Bleeding (cc.)	180	242
Admission (hours)	45	43
Intraop. Complications (%)	10	7.7
Postop. Complications (%)	**20**	**13.5**

Desai MM et al., J Urol 2005 (Gill)

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Size

Laparoscopic nephrectomy in renal tumors T1 and T2

141 Extended nephrectomies/radicals

Higher Bleeding with increased rate of transfussion
Higher surgical time
Large surgical incision
Open Conversion 1 vs 12 % (p=0.013)
Intraoperative Complications 5 vs 19 % (p=0.006)

Postoperative complication rates and similar hospital stay

Gong EM et al, Urology 2006

Size

Laparoscopic nephrectomy in T2

	Laparoscopy		Open surgery
	Tumors of 7 cm	Tumors > 7 cm	Tumors > 7 cm
Number	166	65	34
Bleeding	100 ml	200 ml	higher
Surgery time	=	=	extended
Analgesia	=	=	higher
Admission	=	=	prolonged
Complication rate	=	=	
Mean size	7 cm	9.2 cm	9.9 cm

Steinberg AP et al. J Urol 2004

Size

Laparoscopic nephrectomy in tumors > 10 cm

Mean age (years), mean 61
Gender ratio: men, n (%) 74 (63.8)
ASA score, n (%) 21 (18.4)
Charlson Comorbidity Index score 2 (0-11)
BMI (kg/m2), mean SD 27.8 / 5.8

Operative time (min), median (IQR) 180 (130-211)
Blood loss (mL), median (IQR) 200 (100-500)
Tumor size (cm), median (IQR) 11 (10.2-17)
Hospital stay (days), median (IQR) 6 (4-7.5)

Verhoest et al. Clin GenitoUrinary Cancer 2016

Size

Laparoscopic nephrectomy in tumors > 10 cm

Conversion to open surgery, n (%) 24 (20.7)
Bleeding 13 (54.2)
Intraoperative complications, n (%) 19 (16.4)
Medical complications, n (%) 16 (13.8)
Surgical complications, n (%) 16 (13.8)
Blood transfusion, n (%) 15 (12.9)
Major complications: Clavien 3, n (%) 10 (8.6)
pT stage
pT2b 44 (39.6)
pT3a 65 (58.6)
pT4 2 (1.8)
The majority Fuhrman grade 3-4 and Clear cell cancers

Verhoest et al. Clin GenitoUrinary Cancer 2016

Size

ROSULA Collaborative Group

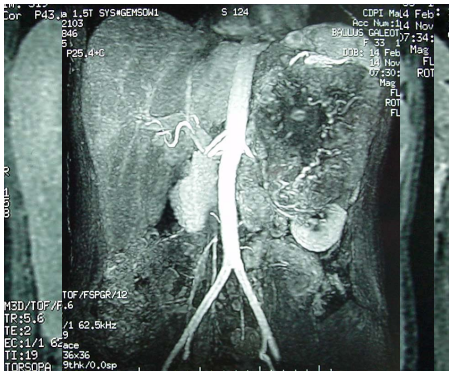
ROBOTIC VS LAPAROSCOPIC NEPHRECTOMY IN cT2 OR MORE DISEASE

941 patients (404 robotic and 537 laparoscopic)
No difference in terms of gender, age and tumor size

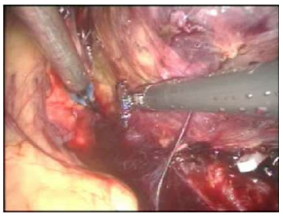
Operative duration longer in RRN (185 vs 126 min)
Length of stay shorter for RRN (3 vs 5 days)
More advanced disease in RRN (52.5 vs 24.2%)
Higher grade in RRN (49.3 vs 30.4 %)
Rate of positive nodal disease higher in RRN (5.4 vs 1.) %)

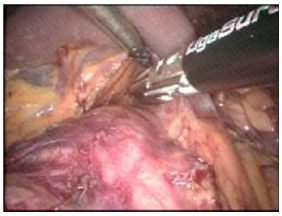
Perioperative complications similar

Anele et al. World J Urol 2019



Left nephrectomy in T3





Locally advanced RCC with thrombus level I in the r.vein

Correct Indication?

N= 12 patients

2 cases were converted to open nephrectomy

4 cases were diagnosed through intraoperative ultrasound

No intraoperative complications were objectified

Kapoor A et al. Urology 2006

Locally advanced cancer T3

N: 36 patients

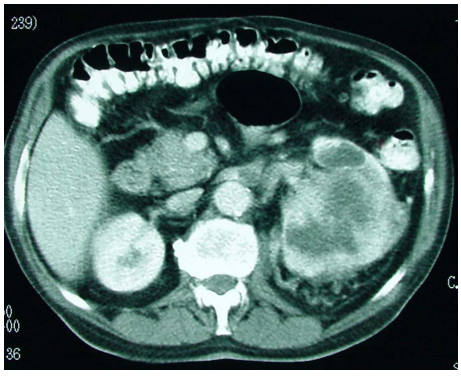
27 pT3a
7 pT3b

Mean surgical time: 4 hours
Blood loss; 250 cc

2 pT4

Conversion to open surgery

Wille Eur Urol 45: 496, 2004



Nephrectomy with thrombous in renal vein

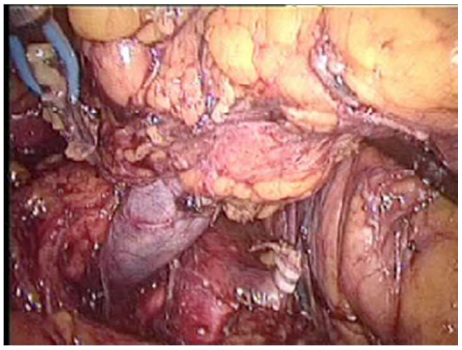


Imagen: Dr. Rosales

Cytoreductive nephrectomy

Laparoscopy versus open cytoreductive nephrectomy in metastatic patients for renal carcinoma

	Laparoscopy	Open
Number	22	42
Admission (days)	**2.3**	6.1
Surgical bleeding (cc)	**288**	1228
Systemic therapy (days)	**36**	61
Survival rate in 1 year	61 %	65 %

Rabets JC et al. Urology 2004

Cytoreductive nephrectomy

Experience of M.D. Anderson Cancer Center

N= 38 patients

Higher bleeding and days in hospital

There were no differences related to complications, time or surgical interval of the systemic therapy (41 days) between the open and laparoscopic surgery

Matin Sf et al. Urology 2006

Cytoreductive nephrectomy

Cytoreductive laparoscopy vs nephrectomy non metastatic

	Laparoscopy + Metastasis	Laparoscopy (clinic T2)
Number	22	25
Size (cm)	8	9.6
Surgical time (hours)	3.1	3.2
Hospital stay (days)	1.7	1.6
Operative bleeding (cc)	285	308
Systemic therapy (days after surgery)	36	

Finelli A et al. BJU Int 2004

Age

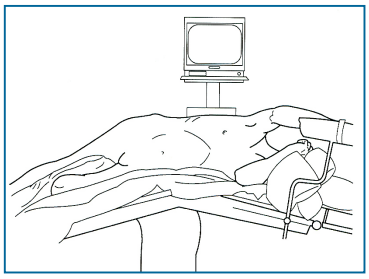
Renal surgery in patients > of 80 years

	Laparoscopy	Open	P value
Surgical time (min)	210	175	0.1
Bleeding (cc)	150	125	0.8
Specimen weight (gr)	568	292	0.04
Diet (days)	**1**	4	0.004
Analgesia (mg)	**14**	326	0.004
Hospital stay (days)	**2**	6	<0.001
Convalescence (days)	**14**	42	<0.001

Hsu TH et al., Urology 1999

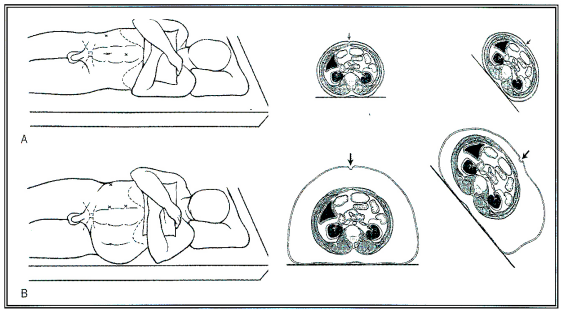
Obesity

Patient position



Obesity

Role of the lateral decubitus position during laparoscopic surgery in obese patients



Obesity

Complications in laparoscopic surgery regarding BMI

	BMI 30 or higher	BMI lower than 30	P value
Surgical time (min.)	280	241	0.003
Estimated bleeding (cc)	230	109	0.0001
Transufsion rate (%)	6.8	0.8	0.032

Similar conversion rate, analgesia, hospital stay, early intake and complications

Anast JW et al., J Urol 2004

Obesity

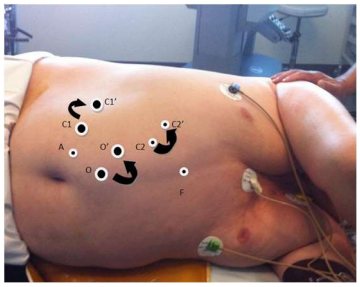
Benefits of laparoscopy in obese patients

Patients with body mass index >30 benefit more by laparoscopic surgery compared to thinner patients in regards to analgesic requirements and global morbility

Klingler HC et al., Eur Urol 2003

Obesity

Role of the lateral decubitus position during laparoscopic surgery in obese patients



Arfi et al., Curr Urol 2014

Obesity

Role of the lateral decubitus position during laparoscopic surgery in obese patients

215 patients: 30 with a BMI over 30 Kg/m2

	Non-obese patients BMI < 30 (kg/m²)	Obese patients BMI ≥ 30 (kg/m²)	p
Number of patients	163	52	
BMI, kg/m	23.6 ± 3.2	35.4 ± 5.8	< 0.001
Age, years	58.6 ± 16.3	60.4 ± 12.1	0.378
Ratio male/female, n	81/82	25/27	0.839
Ratio left/right	84/79	25/27	0.664
ASA score	2.0 ± 0.8	2.3 ± 0.6	0.006
Type 2/Type 1 diabetes, n (%)	9 (5.5%)	13 (25%)	< 0.00
HA, n (%)	80 (49%)	34 (65%)	0.049
History of abdominal surgery, n (%)	99 (61%)	31 (60%)	0.869
Arteriopathy, n (%)	17 (10%)	13 (25%)	0.009
COPD/SAS, n (%)	15 (9%)	13 (25%)	0.004
Anticoagulant/Antiplatelet use, n (%)	25 (15%)	14 (27%)	0.049

ASA Score
Diabetes
Arteriopathy
COPD
Anticoagulant

No differences. Slight not significant increase of hernias

Arfi et al., Curr Urol 2014

Disadvantages of laparoscopic surgery

Laparoscopic port cell implantation

Incidence: 0,18 – 4%

- 7 after laparoscopic nephroureterectomy
- 4 after laparoscopic pelvic LDN
- 3 after laparoscopic radical nephrectomy
- 1 after laparoscopic partial cystectomy

Risk factors for metastasis in the ports and recurrence

1. High grade and stage tumors
2. Incorrect trocar fixation. Avoid gas leaks
3. "Morcellation"
4. Intraabdominal tumor spread
5. No Endobag
6. "Chimney effect" of CO2 between the trocar and the abdominal wall
7. Not to wash the wound with saline

Recomendations to minimize risk of cellular implantation

1. Good trocar fixation. Avoid gas leaks
2. Minimal manipulation of the tumor
3. Avoid "morcellation"
4. Specimen removal by means of Endobag
5. Placing the drainage before deflation
6. Washing the wound with saline

Conclusions

What are the limits of laparoscopic radical nephrectomy?

In locally advanced disease:
- Size (T1-T2-T3a)
- Renal vein involvement (T3b)
- Caval involvement (T3c)
- T4
- Lymphatic involvement (N1-N2)
- Cytoreductive surgery in metastatic patients

Age
Obesity
Previous surgeries
Cell implantation in bloody areas

THANK YOU!

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Wake Forest School of Medicine

Prevention and Management of Infectious Complications in Endoscopic Surgery/Abx Prophylaxis

Jorge Gutierrez M.D
Professor of Urology
Director of Endourology and Stone Diseases

Medical Complications/Endourology

MEDICAL COMPLICATIONS	Incidence %
Fever	10.5-24
Sepsis/multi-organic failure	0.5-4.7
Embolism	0.3-1
Dead	0-1.1

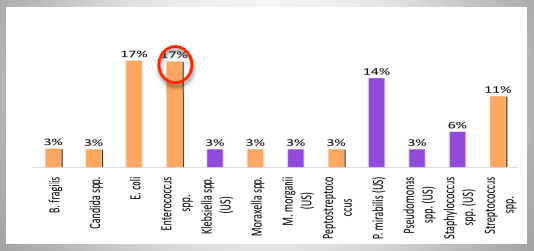
Skolarikos A., Current Opinionin Urology: 2008. 18: 229-234
Seitz, C., Eur Urol: 2012. 61 (1): 146-58
De la Rossette, CROES., J Endourol: 2011; 25 (1): 11-17

Infectious Complications/Endourology Bacteriology

- Pre-Operative urine cultures and understanding of local antibiotic susceptibility patterns are essential
- E. Coli is the most common pathogen followed by Kebsiella and Proteus
- Gram-positive bacteria (enterococcus & stapylococcus must also be considered
- The increasing incidence of resistant pathogens necessitates the development of strategies to reduce the risk of antibiotic resistance
  - Rationalization of the empiric use of antibiotics
  - Limiting antibiotic prophylaxis only to those patients with pre-determined risk

ICUD on Stone Diseases 2014, World J. Urol, 2016

Percentage of struvite stones associated with each organism



De Fazio A, Gupta M, 2014

Bladder, Renal and Stone Cultures

Positive cultures:

- Midstream urine: 11%
- Pelvic urine: 20.4%
- Stone: 35.2%

Same organism:

- Pelvic urine and stone: 85.7%
- bladder and upper urinary tract: none

Risk for urosepsis 4 times higher with pelvic or stone positive cultures.

Mariappan et al, J. Urology, 2005

Infectious Complications/Endourology Pre-Operative Evaluation

- Patient Factors
  - Immunosuppression
  - Chemo/steroids
  - Diabetes mellitus
  - Advanced age, poor nutrition
  - Obesity
  - Renal/liver dysfunction
  - Coexistent infections
  - Prolonged hospitalization
- Urinary Tract Factors
  - Anatomic abnormalities
  - Voiding dysfunction
  - Urinary diversion
  - Urinary tract obstruction
  - Indwelling catheters, stents, nephrostomy tubes

Risk Factors Associated with Postoperative Infectious Complications in GU surgery

Related to patient	Related to urinary tract diseases	Related to procedure
Immunosupression *Malignancy* *Autoimmune diseases* *Chronic corticosteroid use* *Diabetes Mellitus* *Poor nutritional status* *Severe kidney or liver dysfunction* Advanced age Female patients Distant coexistent infection Prolonged hospitalization	Chronic bacteriuria Voiding dysfunction Urinary diversion Obstruction Stone disease Indwelling catheters Endogenous material (ureteral stents) Anatomic anomalies Impaired urinary flow	Stone disease management Incisional therapy Long lasting surgery Involvement of genital tract Involvement of gastrointestinal tract Prosthesis

Patel, Gutierrez: Smith's Text Book of Endourology, 4th Edition, 2018

Infectious Complications/Endourology Pre-operative Management

- Patients with a positive culture must receive pre-op antibiotics tailored to culture-specific organisms
- If UTI is associated with urinary obstruction, one must place a ureteral stent or nephrostomy tube
- If UTI is related to urinary tract or stone bacterial colonization, culture-specific antibiotics must be administered orally (5-7 days) ore IV 24 hours pre-op
- A persistently positive urine culture in patients with a ureteral stent or nephrostomy tube may require replacing the device and re-evaluating urine culture before surgery

Prevention of Infectious Complications WF Protocol

- All stone patients will have a urine sample for urinalysis during clinic visit.
- Patient who are scheduled for surgery and have moderate leucocytes will have a culture done
- Prior negative urine culture older than 30 days will be repeated
- If the patient lives in town:
  - Write an order in Epic for *external* UA/CS for the patient
  - Patient will come by the clinic to leave a urine sample and have a urine culture rechecked

Prevention of Infectious Complications WF Protocol

- If the patient lives out of town and cannot come to clinic:
  - Write/Print an order in for *external* UA/CS for the patient
  - Prepare a fax cover sheet to accompany the order: Fax number……, or via mail
  - Instructions to Patient:

    Leave a mid-stream, clean catch specimen (teach patient how to take sample)

    Request the results of the UA/CS be faxed/mailed to the clinic using the fax cover sheet provided

Prevention of Infectious Complications WF Protocol

- Labs charts review for patients scheduled for surgery 2 weeks/10 days before the procedure.
- If labs have not been updated, patient will be contacted (Att*endee, Physician Assistant, Scheduler*) and results will be requested.
- Patient will be advised that surgery may be suspended/deferred if lab results are not in the patient chart one week before surgery.

Obstructive/Infected Stones WF Pathway of Care

- Initial evaluation ED

  -acute treatment and support

  -Non-contrast abdomen Ct (Low dose protocol/Item Pending)
- Urology evaluation

  -resident on call/consultation (<1 hour)
- Decompression of collecting system
- Definitive stone treatment delayed after urinary sepsis resolved

Obstructive/Infected Stones Kidney Decompression

- Urology Decision
  - patient general conditions/anatomy
  - stone characteristics (size, location)
- Ureteral stents
  - -Urology
  - -ureteral stones <10 mm
- Percutaneous nephrostomy tube
  - -Urology or Intervention Radiology
  - -impacted ureteral stones >10 mm, renal stones
  - -retrograde stent placement not anticipated

Obstructive/Infected Stones Management Pots/Decompression

- Urine sample/culture-antibiogram sensitivity
- Antibiotics regime revisited following culture sensitivity findings
- Admitted to hospital services
  - -Urology/Internal Medicine/Intensive Care (level of service needed)
- Re-culture of urine before definitive treatment
- Definitive surgical treatment. No recommendations for MET
- Surgical treatment discussion based on guidelines recommendations

Prevention of Infections in TURP/TURBT

1 Identify high risk patients
2 Discard active UTI pre-procedure
3 Obtain a preoperative negative urine culture (ideally)®
4 Antimicrobial prophylaxis (AMP) in all cases:*
- Maintain closed the urinary drainage system
- Avoid prolonged catheterization (>3 days)

~ Applicable to other transurethral procedures with manipulation
® In chronic bacteriuria or catheterized patients administer 3-7 days of culture-sensitive antibiotics before surgery
**For TURBT EAU guidelines recommends AMP only in presence of risk factors or large and/or necrotic tumors*

Patel, Gutierrez: Smith's Text Book of Endourology, 4th Edition, 2018

Infectious Complications/SWL

Incidence

- UTI after uncomplicated SWL is <1% rising to 2.7 % during treatment of staghorn stones
- Risk of sepsis increases in the presence of bacteriuria prior to SWL, especially with obstruction

Prophylactic antibiotics only recommended in high-risk stone groups

- N-Tubes
- History of recent UTI or sepsis
- Recent instrumentation
- Positive urine cultures

Infectious Complications/SWL Recommendations

Prevention of Infection / Sepsis in SWL	LOE	Grade
The risk of sepsis increases in the presence of bacteriuria prior to SWL	II	A
Abx prophylaxis is not necessary for SWL in patients with no or low risk	I	A
Prophylactic Abx recommended only in high-risk stone patients eg: infection stones, recent instrumentation, nephrostomy tubes, positive urine cultures or those with a history of recent UTI or sepsis	I	A

ICUD on Stone Diseases 2014, World J. Urol, 2016

Prevention of Infections in ESWL

1 Identify risk factors
2 Discard active UTI pre-procedure
3 Obtain preoperative negative urine culture (ideally)®
4 Antimicrobial prophylaxis (AMP) if one the following:**
- Obstruction
- Presence of an indwelling stent or catheter
- Infection stones
- Periprocedure stone or urological manipulation (Double J stent insertion)

® In bacterial persistence or chronic bacteriuria administer at least 3 days of culture-specific antibiotics before SWL
***AUA guidelines recommends AMP in all cases*

Patel, Gutierrez: Smith's Text Book of Endourology, 4th Edition, 2018

Infectious Complications/URS Incidence

- CROES Ureteroscopy Global Study reported a multicenter trail in 11,885 patients
- Incidence of postoperative infectious events
  - Post- operative fever 1.8%
  - Urinary tract infection 1.0%
  - Sepsis 0.3%

de la Rossete, J. Endourol, 2014

Infectious Complications/URS Antibiotic Prophylaxis

- Consider antibiotic prophylaxis for any ureteroscopic intervention for the treatment of urinary tract calculi
- Singe prophylactic oral dose of levofloxacin reduced risk of post-op bacteruria from 12.5% to 1.8%

Knopf, et al, Eur Urol, 2003

Infectious Complications/URS Recommendations

Prevention of Infection / Sepsis in URS	LOE	Grade
Antimicrobial prophylaxis in all patients	II	A
Never perform stone manipulation in the presence of active UTI – Relieve obstruction, treat infection, proceed with staged treatment	I	A
In patients with chronic bacteruria, administer at least 5 days of culture-specific Abx prior to instrumentation	II	B

ICUD on Stone Diseases 2014, World J. Urol, 2016

Prevention of Infections in URS

1 Identify high risk patients
2 Discard active UTI pre-procedure
- *Never perform stone manipulation or incision therapy in active UTI! Relieve urinary obstruction, treat infection and carry out a staged treatment*

3 Ensure a preoperative negative urine culture (ideally)®
4 Antimicrobial prophylaxis in all cases
5 Maintain low intrarrenal pressure during procedure
- *Options: Periodic drainage through ureteroscope, use of ureteral access sheath or angiographic catheter. Continuous or intermittent bladder drainage*

® *In chronic bacteriuria administer at least 3 days of culture-sensitive antibiotics before instrumentation*

Patel, Gutierrez: Smith's Text Book of Endourology, 4th Edition, 2018

Infectious Complications/PCNL Incidence

- Fever 21.0 – 39%
- Sepsis .3 – 9.3%
- Reasons for UTI after PCNL
  - Release of bacteria during stone fragmentation
  - Introduction of bacteria through nephrostomy tract

Infectious Complications/PNL Risk Factors for Fever-Sepsis-SIRS

- Pre-operative factors
  - Hydroureteronephrosis
  - Pre-op nephrostomy tube
  - Complex stone burden
  - Neurogenic bladder
  - Reconstructed urinary tracts
  - Diabetes mellitus
  - Immunosuppression
  - Female gender

Gutierrez, CROES, World, J. Urol, 2011

UTI & PCNL
Risk Factors for Fever- Sepsis

- Intra-operative factors
  - Number of access tracts
  - Operative time
  - Volume of irrigation fluid
  - Purulent urine during percutaneous puncture
  - Bleeding during surgery

Gutierrez, CROES, World, J. Urol, 2011
Razvi, Denstedt, J. Urol, 2016

Infectious Complications/PCNL
Antibiotic Regimens for PCNL

- When the pre-op urine culture is negative, a single dose appears to be as effective in preventing post-operative infections as multiple doses, irrespective of antibiotic used.

Bootsma, et al, Eur Urol, 2008

Infectious Complications/PCN
Surgical Recommendations

- Keep intra-renal pressure low: <30 mm hg
- Use diuretics at the beginning of irrigation and repeat every hour
- Intermittent suction/irrigation
- Multiple simultaneous tracts (continuous drainage)
- Limited lithotripsy/irrigation time
- Staged procedure
  - * 1st stage: drainage/kidney decompression
  - * 2nd stage stone fragmentation/removal

Negrete O, Gutiérrez J, J. Endourol, 10:2009; 1757-1762
Patel M, Gutierrez J, Smith's, Textbook of Endourology, 4th Edition

Infectious Complications/PCNL
Recommendations

Prevention of Infection / Sepsis in PCNL	LOE	Grade
A urine culture should be performed in all patients prior to PCNL	III	A
Patients with a positive pre-op culture should be treated prior to PCNL	II	A
All patients who undergo PCNL should receive antibiotic prophylaxis	III	B
When Abx prophylaxis is used, no specific regimen can be recommended – prophylaxis should be chosen according to regional antibiogram and safety of Abx agents	III	A

ICUD on Stone Diseases 2014, World J. Urol, 2016

Prevention of Infections in PCNL

1 Identify high risk patients
2 Discard active UTI pre-procedure
- *Never perform stone manipulation or incision therapy when active UTI!*

3 Ensure sterile urine preoperatively (ideally)®
4 Antimicrobial prophylaxis in all cases
5 Stop procedure If purulent fluid is obtained at puncture, leave a nephrostomy tube and stage treatment*
6 Maintain low intrarrenal pressure during procedure
- *Use only enough irrigation to maintain adequate visibility*
- *Use a wide renal access sheath, ideally 2-4 Fr. wider than nephroscope*

7 Limit quantity of irrigation fluid and operative time

® *In chronic or asymptomatic bacteriuria administer at least 7 days of culture-sensitive antibiotics before surgery*
**Obtain pelvic urine culture and treat infection completely*

Patel, Gutierrez: Smith's Text Book of Endourology, 4th Edition, 2018

Recommended Antibiotic Prophylaxis

Recommended Antibiotic Prophylaxis

Endourologic surgery and shock wave lithotripsy						
Shock wave lithotripsy	All	If risk factors	Fluoroquinolone or TMP–SMX or 2nd/3rd generation cephalosporin	Aminoglycoside + Ampicillin or Amoxicillin/clavulanate	≤24 h	*Patients with ureteral stent, nephrostomy Obstruction and infection stone
TURP/TURBT	All	If risk factors	Fluoroquinolone or TMP–SMX or 2nd/3rd generation cephalosporin or aminopenicillin/BLI	Aminoglycoside + Ampicillin or 1st generation cephalosporin or Amoxicillin/clavulanate	≤24 h	**Consider in large necrotic tumors
Ureteroscopy	All	If risk factors	3rd/4th generation cephalosporin or TMP–SMX or aminopenicillin/BLI or Fluoroquinolone	Aminoglycoside + Ampicillin or 1st generation cephalosporin or Amoxicillin/clavulanate	≤24 h	
Percutaneous renal surgery	All	All	3rd/4th generation cephalosporin or TMP–SMX or aminopenicillin/BLI	Ampicillin/sulbactam or Fluoroquinolone or 1st generation cephalosporin	≤24 h	Length of short course to be determined, intravenous route suggested

Physipathology of Urinary Tract Infection and Sepsis

- Bacteria colonization or active infection
- Injury to the urinary tract
- Urinary bacteria enter the bloodstream via pyelovenous-lymphatic and pyelotubular backflow and forniceal rupture
- Stone manipulation
- Destruction (Inactivation) of bacteria and liberation of endotoxins
- Systemic inflammatory response

Negrete O, Gutiérrez J, J. Endourol, 10:2009; 1757-1762

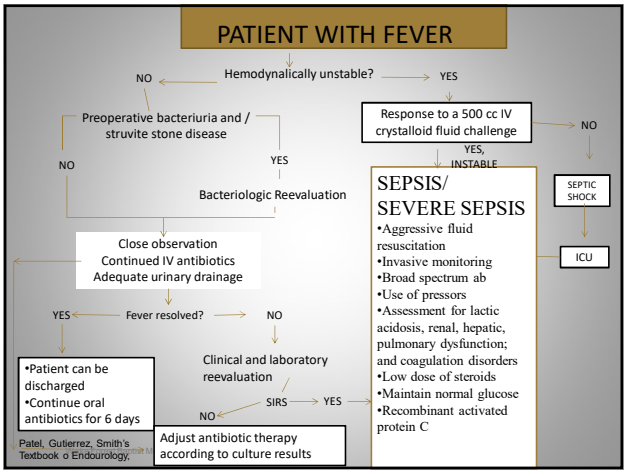
Intraoperative Urine Cultures

- **Statement 4: Clinicians are required to obtain a urinalysis prior to intervention. In patients with clinical or laboratory signs of infection, urine culture should be obtained. *Strong recommendation; Evidence Level Grade B***
- **…..** A urine culture should be obtained if UTI is suspected …..the patient should be prescribed appropriate antibiotic therapy based on sensitivity results…
- …. there can be discordance between preoperative voided urine cultures…compared to urine proximal to an obstructing stone….
- ….. Intraoperative urine cultures should be obtained, if technically feasible, from urine proximal to the stone **if infected urine is suspected at the time of intervention**
- …. stone cultures may be obtained, especially in cases of suspected infection-related stones, **in order to help guide postoperative therapy....**potential discordance between stone cultures and preoperative voided urine cultures….

AUA, Guidelines on Stone Surgery, 2016

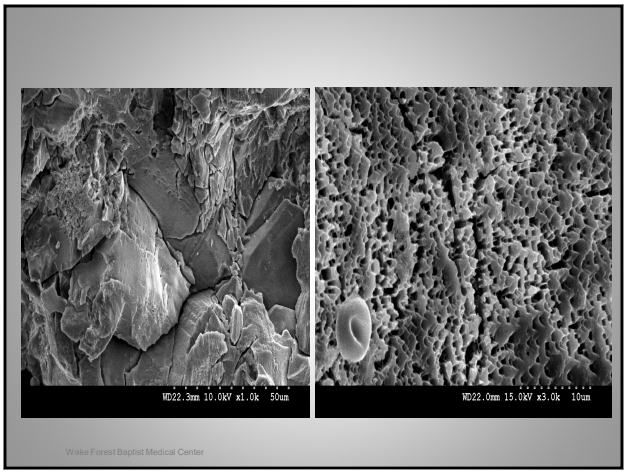
RPUC and SC during Stone Surgery

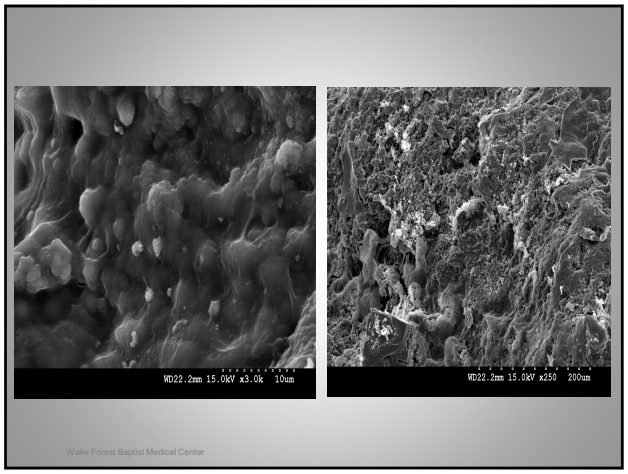
- The rate of discordance between urine and stone cultures up to 25%
- The pathogen causing post-operative infection had a significantly higher correlation with the organism grown on stone culture than the preoperative urine culture
- Gram-positive organisms have a higher incidence in preoperative urine and stone cultures
- Positive peri/intraoperative urine cultures may assist the urologist in directing appropriate antibiotics to prevent potential urosepsis in post-PCNL patients
- MSUC, RPUC, and SC may not demonstrate any significant association with the occurrence of SIRS
- **Collect RPUC and SC samples during ureteroscopy and PCNL to identify the potential organisms in patients at risk for infection/sepsis including positive MSUC results**



Infectious Complications What we don't know?

- Bacteria interaction/behavior in renal urine and inside stones
- How bacteria protect themself, potential biofilm formation
- What really happen after stone fragmentation, potential intra-bacterial protein (endotoxins) liberation?





Infectious Complications/Endourology
What can help to Prevent Infections?

- Adequate preoperative evaluation
- Identify pre-operative risk factors (patient and urinary tract)
- Adequate assessment of culture data and adherence to appropriate guidelines
- Consider surgical modifications base on patient risk
- Early identification of an infectious problem
- Be aggressive with the medical treatment
- Ask for help

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