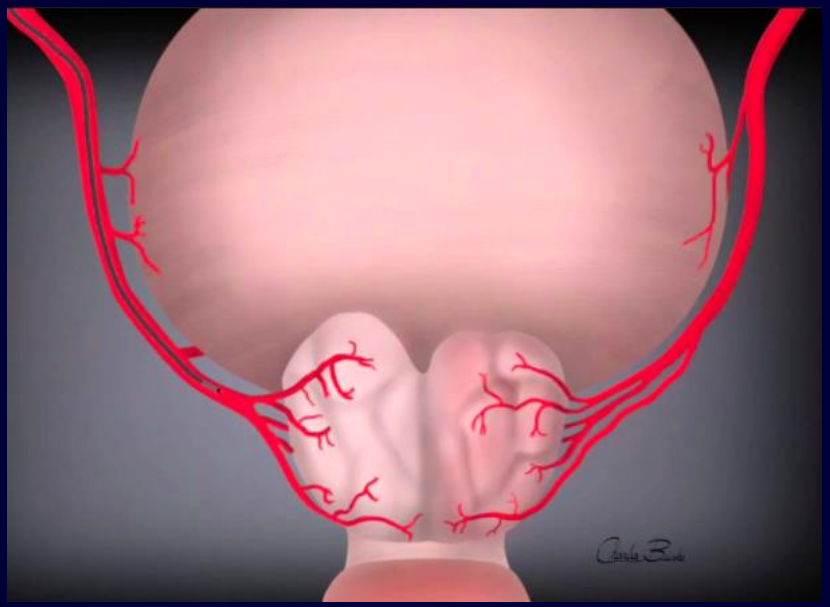
Prostate Artery Embolization: A Minimally Invasive Option for the Treatment of BPH



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BRG
BOCA RADIOLOGY GROUP

Educational Objectives

To understand:

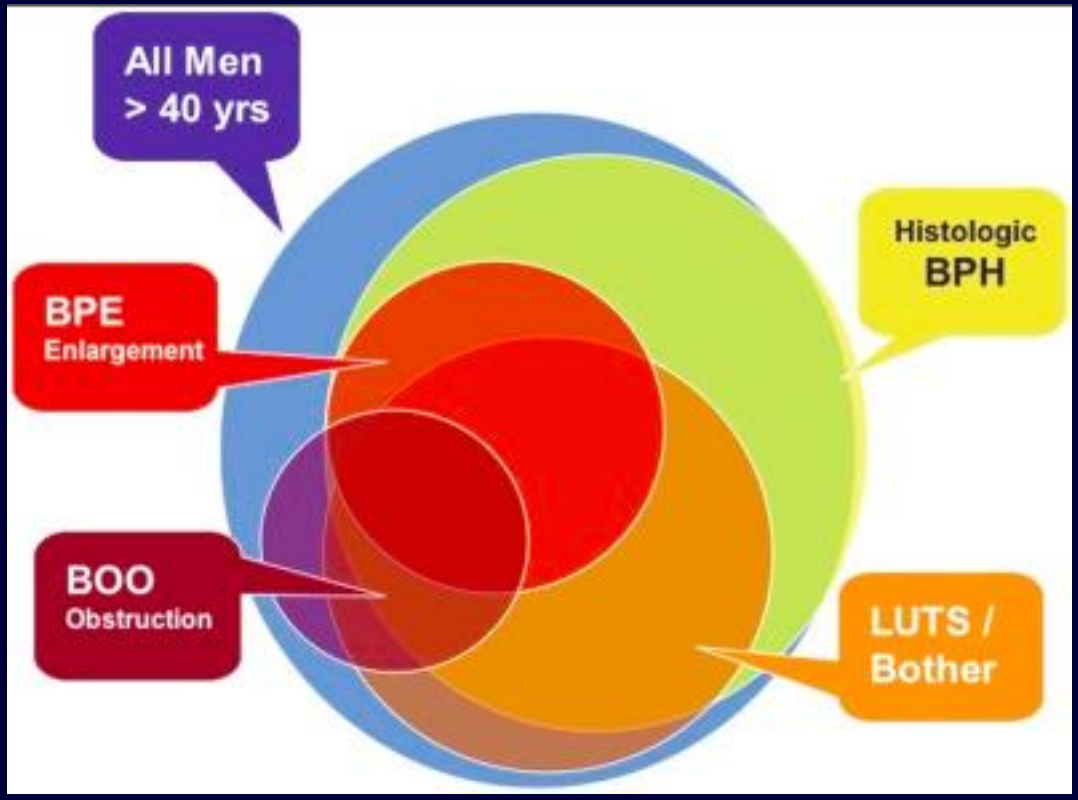
- Epidemiology and pathophysiology of Benign Prostatic Hyperplasia (BPH)
- Origin and current utilization of Prostate Artery Embolization (PAE)
  - Minimally invasive treatment option
- Identification of patients suitable for PAE
- PAE procedural safety and efficacy

BPH Epidemiology

Benign Prostatic Hyperplasia (BPH):

- One of the most common health conditions of aging men wordwide
- High histologic prevalence at autopsy
  - 50% in pts <60 yo
  - 90% in pts <85 yo
- At age 70, 40% men symptomatic and by age 75, 50%
- 4.5 million office visits in 2009
- Direct cost of 1.1 billion dollars

BPH Epidemiology



Relationship between histologic hyperplasia, clinical symptomatology (LUTS), benign prostatic enlargement and bladder outlet obstruction

BPH Pathophysiology

Histopathology:

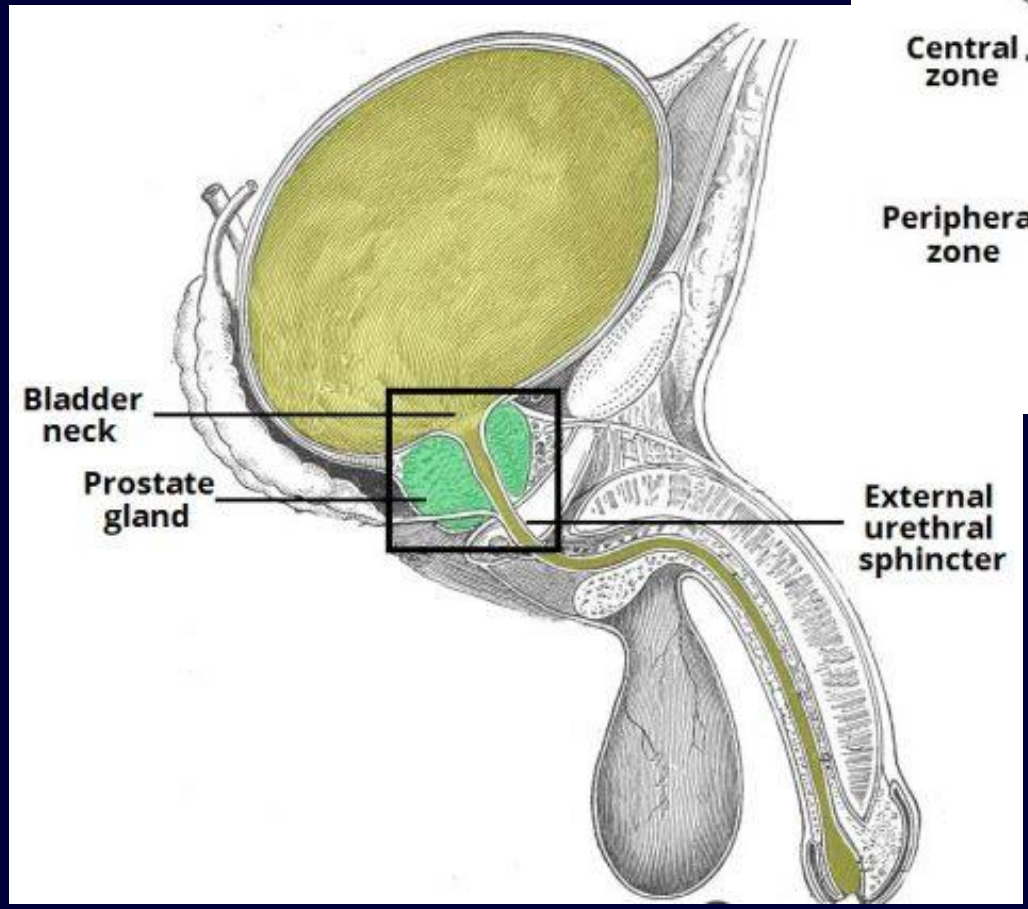
- Increased number epithelial and stromal cells
  - Molecular etiology of process remains uncertain
  - Due to cellular proliferation or impaired programmed cell death
  - End result is cellular accumulation
- Multifactorial process
  - Androgens
  - Estrogens
  - Stromal-epithelial interaction
  - Growth factors
  - Neurotransmitters

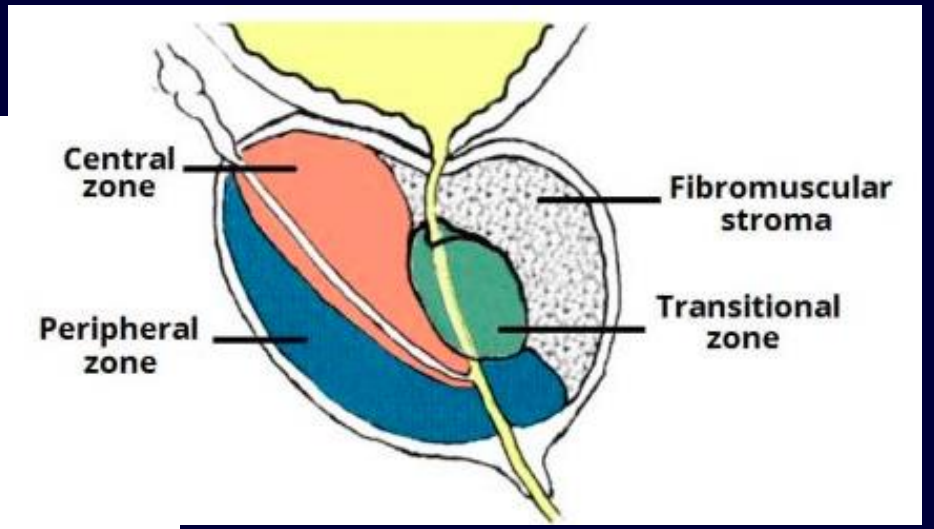
BPH Pathophysiology

Histopathology:

- Hyperplasia
  - Androgens
    - Required for normal cell growth and differentiation
    - But, actively inhibit cell death
    - Prostate continually responds to androgens
  - Aging
    - Development of well-differentiated cells reduced
    - Reduced cell death rate
  - Stromal-epithelial interactions
    - Prostatic stroma induces epithelial cell development
- Inheritable, genetic component

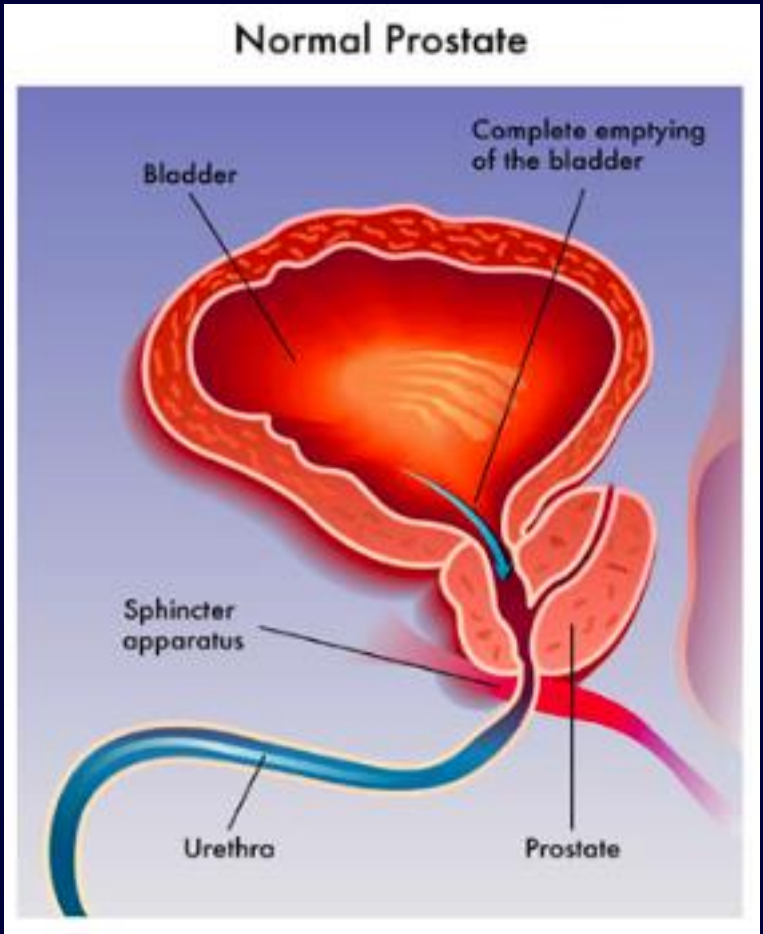
BPH Pathophysiology

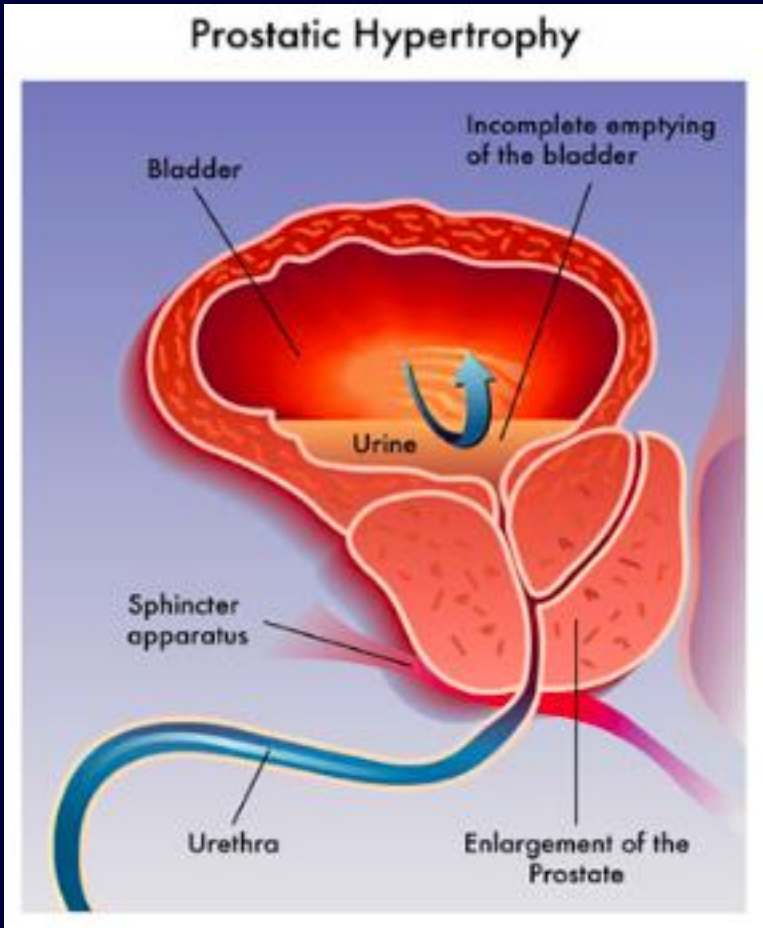




Transitional zone surrounding urethra, 5-10% of normal prostate volume, contains glands that undergo benign hyperplasia

BPH Pathophysiology





BPH Pathophysiology

Lower Urinary Tract Symptoms (LUTS):

- Voiding / Obstructive
  - Hesitatancy
  - Straining
  - Prolonged voiding or weak flow
  - Terminal dribbling
  - Retention
  - Overflow incontinence
- Storage / Irritative
  - Frequency or nocturia
  - Urgency
  - Urge incontinence

Untreated BPH → urinary retention, recurrent UTI's, hydronephrosis and renal failure

BPH Pathophysiology

International Prostate Symptom Score (IPSS):

- 0-7 = Mild
- 8-19 = Moderate
- 20-35 = Severe
- QOL Score
  - 0 = Delighted
  - 6= Terrible

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
		1	2	3	4	5	
		1 Time	2 Times	3 Times	4 Times	5 Times	
		1	2	3	4	5	
Total I-PSS Score							

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

BPH Treatment

Treatment options:

- Watchful waiting
  - "Self management" – restrict evening fluid, ETOH, and caffeine
- Medical therapy
  - α_1-adrenergic blockers
    - reduce smooth muscle tone in bladder neck and prostate to ↓ BOO
    - dizziness and orthostatic hypotension, possible retrograde ejaculation
  - 5α-reductase inhibitors
    - inhibit conversion of testosterone to dihydrotestosterone, a more potent androgen
    - cause apoptosis of prostatic epithelial cells → volume reduction
    - sexual dysfunction

BPH Treatment

Treatment options:

- Medical therapy
  - antimuscarinic drugs
    - reduces bladder smooth muscle contraction
    - dry mouth, constipation and voiding difficulty
  - phosphodiesterase $_5$ inhibitors
    - decrease smooth muscle tone and contraction in bladder, prostate and penile tissues
    - contraindicated in pts using nitrates

BPH Treatment

Treatment options:

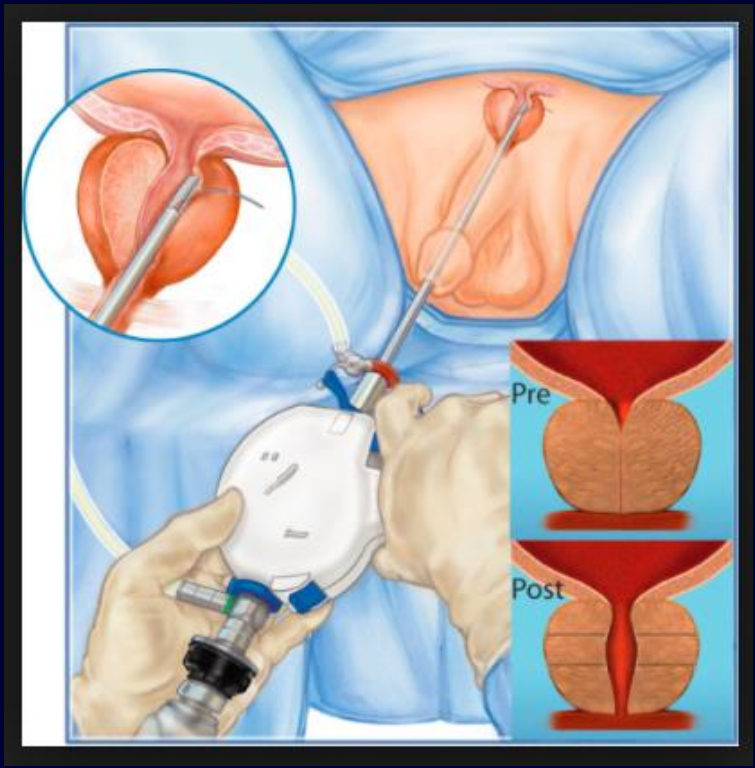
- Traditional surgical interventions, “Gold Standard”
  - TURP and prostatectomy
    - Peri-operative morbidity, incontinence and erectile dysfunction
- Minimally invasive surgical therapies (MIST)
  - Transurethral incision of the prostate (TUIP)
    - If smaller gland, <30mL
  - Thermo-ablative strategies
    - Transurethral microwave therapy
    - Transurethral evaporation of the prostate
    - Transurethral needle ablation
    - Rezum utilizing water vapor

BPH Treatment

Treatment options:

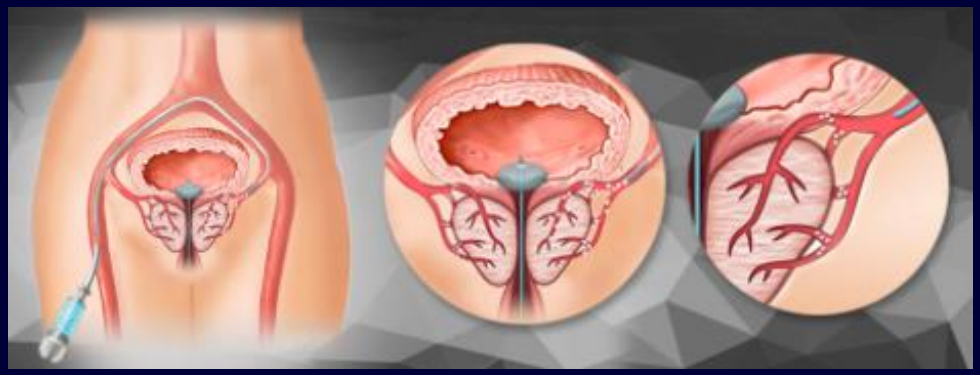
- Minimally invasive surgical therapies (MIST)
  - Mechanical approaches
    - UroLift®
    - Intraprostatic stents

Placement of non-absorbable monofilament sutures into the prostatic urethra through to the lateral lobes with traction, to increase diameter of the urethral channel



Prostate Artery Embolization

Percutaneous, image-guided, highly selective catheter-directed embolization of bilateral prostatic arteries



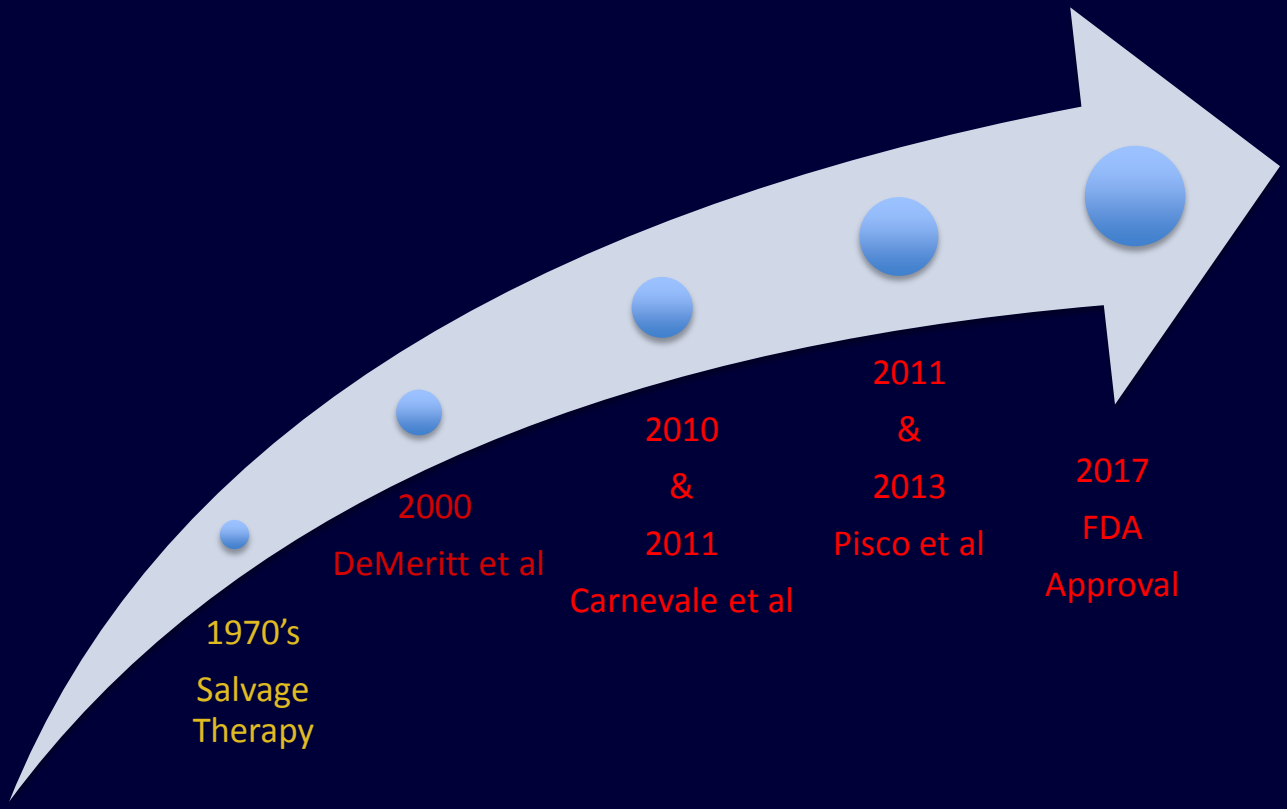
Significant reduction in prostatic blood flow → cessation of hemorrhage & tissue ischemia → inflammatory rxn with cytotoxic edema and leukocytic infiltration

Initial swelling subsides → gland size reduction, decreased tissue density and cystic change

↓

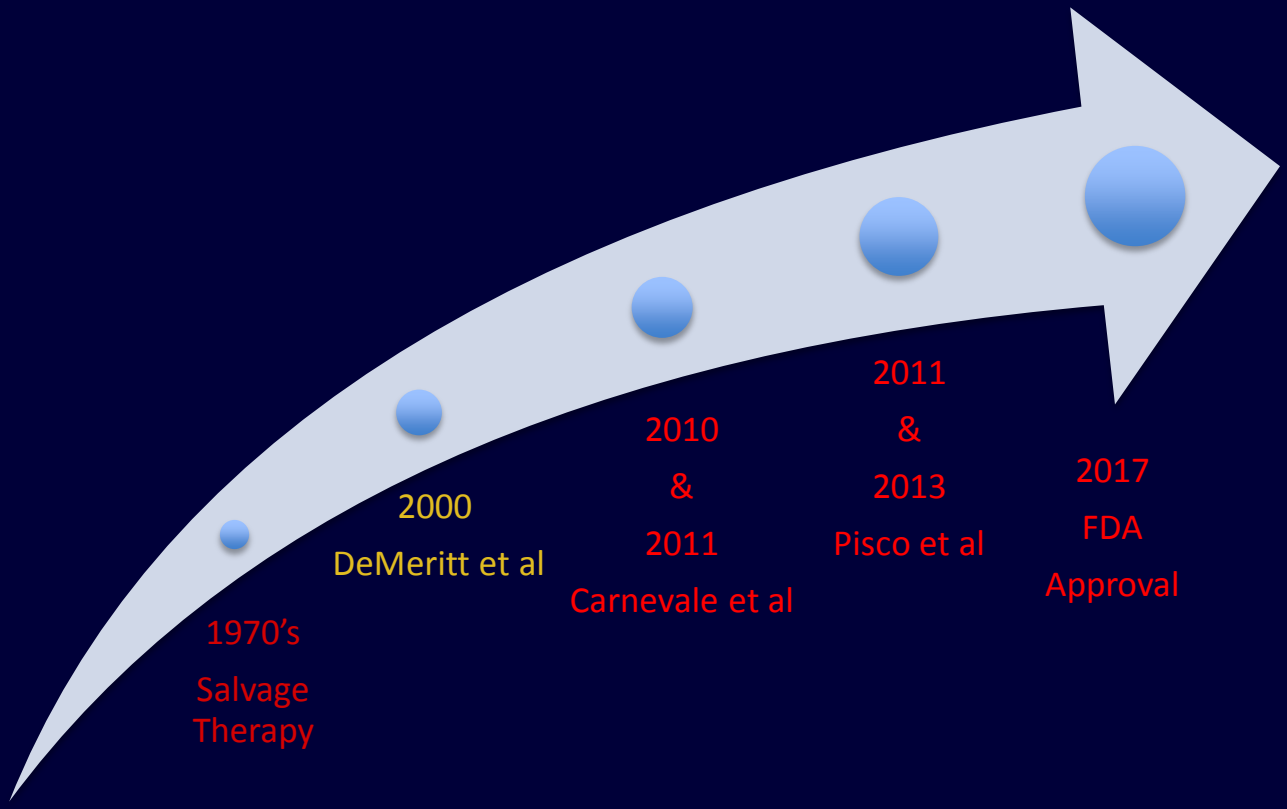
Decreased pressure in prostatic urethra and improved LUTS due to BPH

PAE Origin



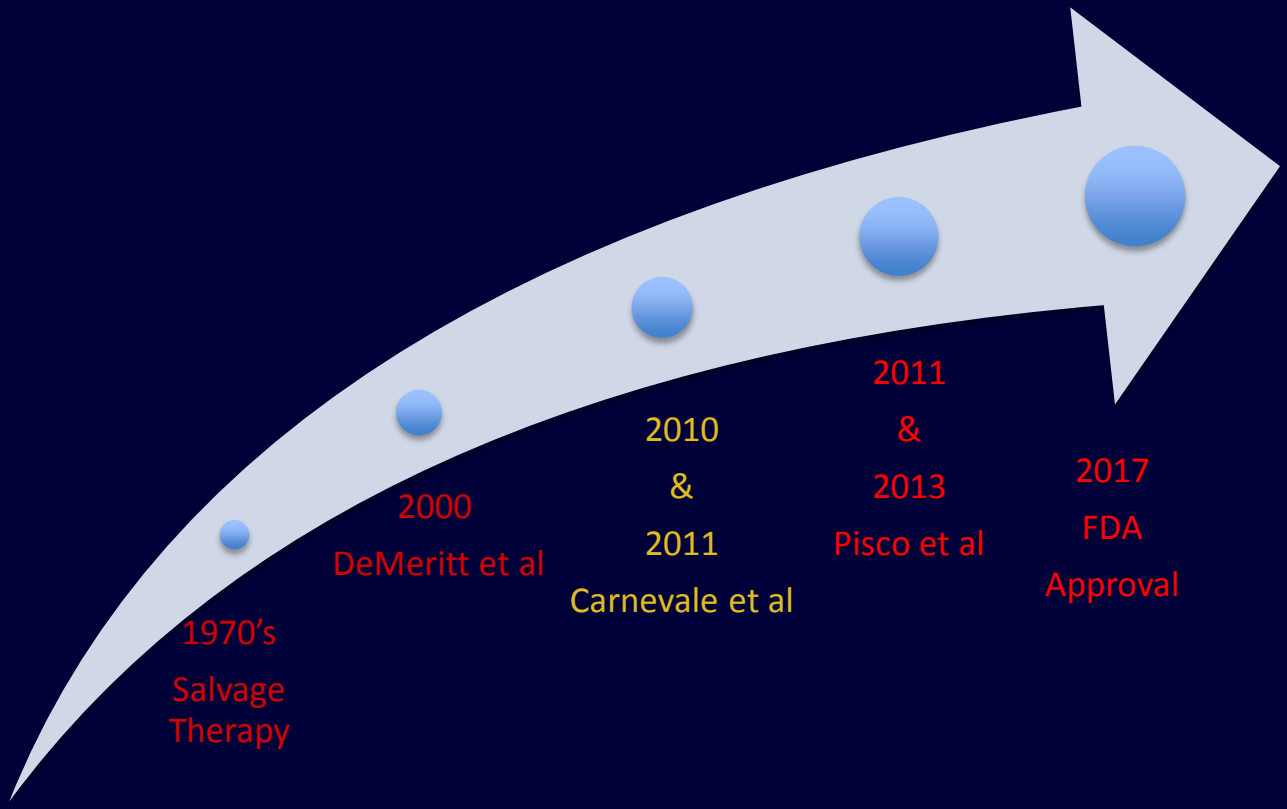
Performed as salvage therapy for vascular injury and hemorrhage s/p prostate biopsy, TURP or open prostatectomy

PAE Origin



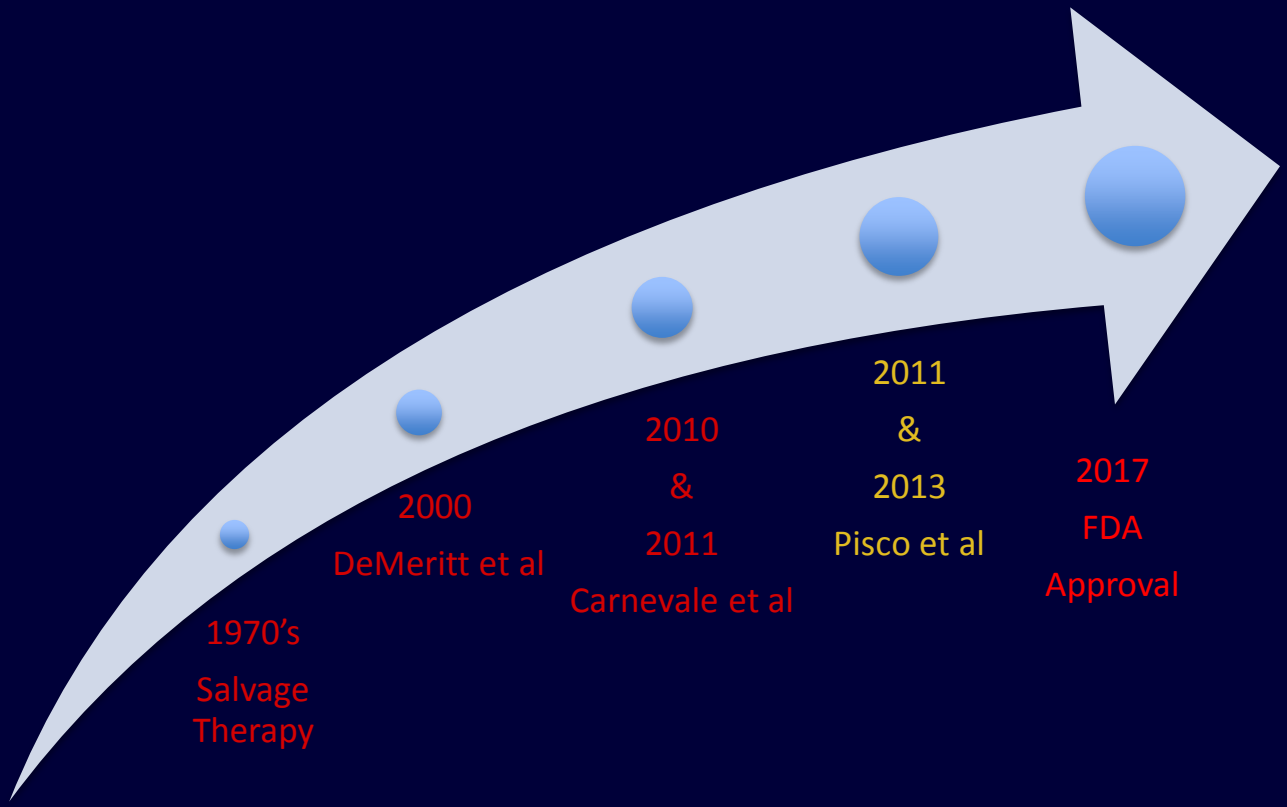
Case Report: 76 yo M with heart disease, prosthetic valve, and prostate volume of 305mL p/w acute urinary retention and hematuria requiring transfusion due to BPH. Sx's refractory to medical and interstitial laser tx so b/l PAE with PVA. Hematuria stopped and at 12 months LUTS significantly improved with 40% reduction in prostate volume and no change in sexual function.

PAE Origin



Preliminary and midterm results of PAE in 2 pts with acute urinary retention due to BPH:
67 yo M voided PPD #15 s/p b/l PAE and remained catheter free with 50% reduction in gland size at 18 months. At 30 months, IPSS score 1 and QoL score 0.
68 yo M s/p unilateral PAE, catheter out PPD #10 and at 18 months, 20% reduction in gland size.

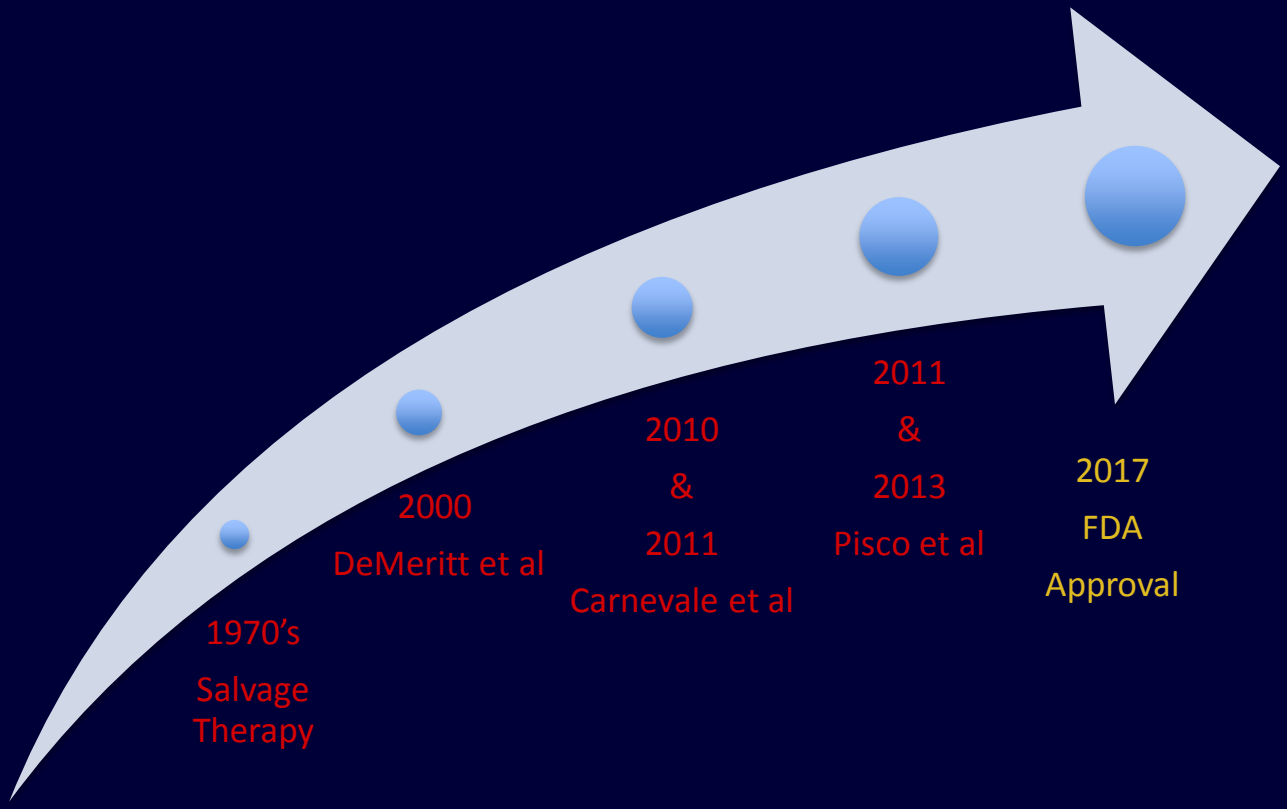
PAE Origin



2011: Feasibility of PAE in 15pts with BPH refractory to medical tx. Mean f/u 8 months, IPSS ↓ 6.5 , QoL ↓ mean 1.14, and prostatic volume ↓ 27%. One complication of bladder wall ischemia.

2013: Prospective study of 255 pts with BPH and mod-sev LUTS refractory to 6 months medical tx. Technical success in 98% pts, clinical success rate of 72% at 36 months.

PAE Origin



FDA Approval June 22, 2017

PAE Origin

MERIT MEDICAL

Merit Medical's Embosphere® Microspheres Receive FDA 513(f)(2) (de novo) Classification for Prostatic Artery Embolization Indication

SOUTH JORDAN, Utah, June 22, 2017 (GLOBE NEWSWIRE) -- Merit Medical Systems, Inc. (NASDAQ:MMSI), a leading manufacturer and marketer of proprietary disposable devices used in interventional, diagnostic and therapeutic procedures, particularly in cardiology, radiology and endoscopy, today announced that it has received 513(f)(2) (de novo) classification from the FDA to expand indication for Merit's Embosphere® Microspheres. The indication now includes prostatic artery embolization (PAE) for symptomatic benign prostatic hyperplasia (BPH).

"Merit's Embosphere is the first embolic agent to receive FDA 513(f)(2) classification for prostatic artery embolization, providing a non-surgical treatment option for millions of men who suffer from BPH," said Fred P. Lampropoulos, Merit's Chairman and Chief Executive Officer.

BPH is an enlarged prostatic gland and can cause lower urinary tract symptoms for more than half of all men in their 60s and as many as 90% of men over age 70.[1] The PAE procedure is performed through a tiny incision in the patient's upper thigh or wrist, and uses Embosphere Microspheres to occlude the prostatic arteries, reducing their blood supply and causing the prostate to shrink and improve symptoms.

Minimally invasive, outpatient treatment option for men with hematuria and/or LUTS due to BPH

PAE Indications

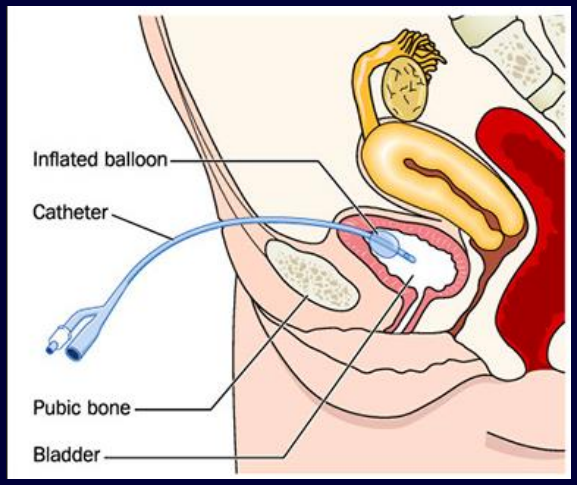
Patient selection:

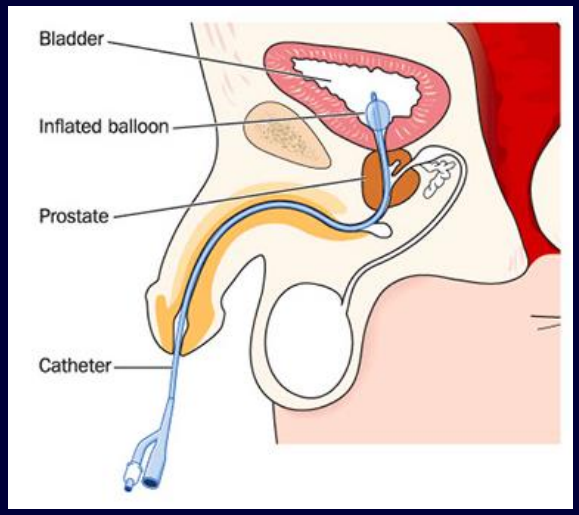
- Non-surgical candidates
  - Refusal of surgery
  - Medical co-morbidities
  - Prostate gland size, greater than 100-150 mL's
- Failure of medical therapy
  - Refractory symptoms despite drug regimen
  - Limited compliance or refusal due to side-effects
  - Contraindication to medical therapy

PAE Indications

Patient selection:

- LUTS
  - IPSS >12 -18 and/or QoL score ≥3
- Prostate volume > 40cm^3
  - “Larger the better”
- Urodynamics
  - Qmax <12-15 mL/s
  - Acute urinary retention
- Catheter dependent pts
  - Foley or suprapubic tube
- Hematuria
  - Inability to tolerate anticoagulation





PAE Contraindications

Ineligible Patients:

- LUTS not due to BPH
- Active infection
  - Chronic UTI
  - Prostatitis
- Prior pelvic radiation
- Renal failure
  - CO_2 as alternative to contrast material
- Neurogenic bladder

Pre-Procedure Work-Up

Interventional Radiology Consultation:

- H&P
- Review of LUTS and/or hematuria
- Evaluation of Cr, coagulation parameters, etc.

Imaging Evaluation:

- Transrectal US or Prostate MRI
  - Determine size
- Optional pre-procedure CTA
  - Sublingual NTG with monitoring by Radiology Nursing staff
  - Determine arterial supply of prostate gland
  - 3D reformatted images for pre-procedural planning

Pre-Procedure Work-Up

Urologic Evaluation:

- Overall eligibility
  - Initial referral to Interventional Radiology
- PSA
  - If abnormal, cancer workup to be performed
- Urodynamic testing
- Medical therapy optimization

TEAM APPROACH to achieve best results for each individual patient

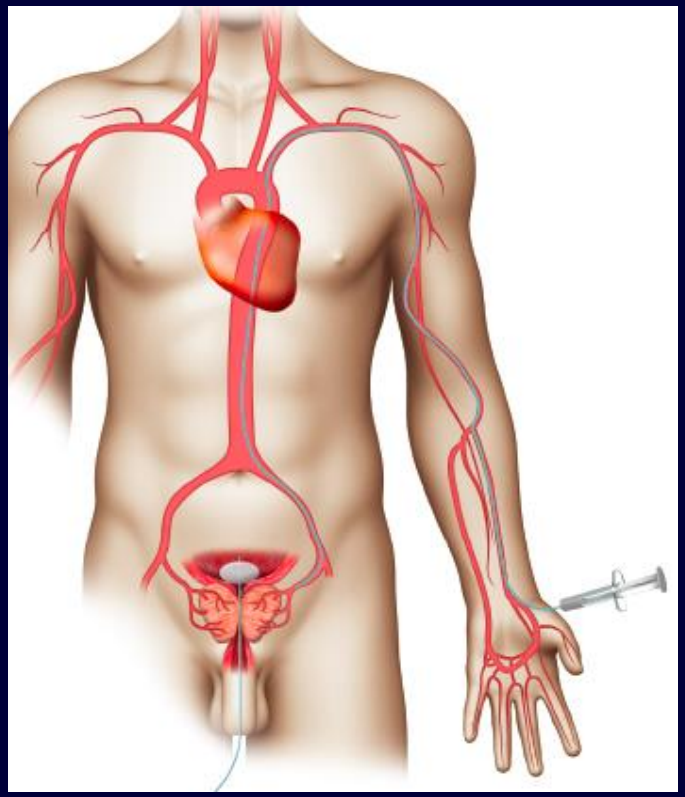
PAE Procedure

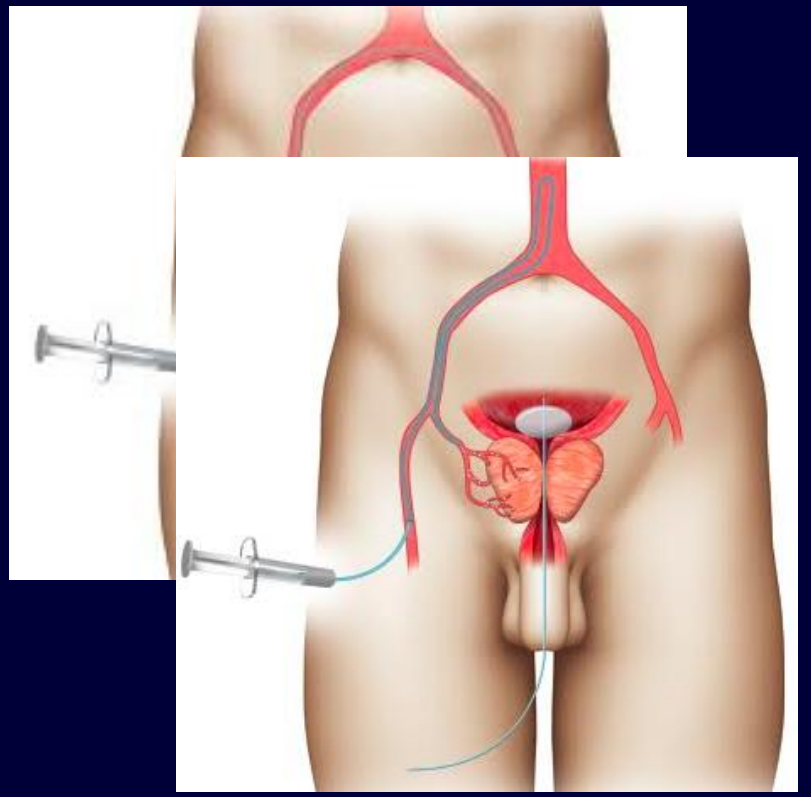
Pre-Procedural/Intra-procedural Care:

- Same-day, outpatient procedure
- Antibiotic phrophylaxis
  - Cipro IV 400mg
- Anti-inflammatory prophylaxis
  - Dexamethasone 8mg IV
- Conscious sedation
  - Versed and Fentanyl
  - Intra-procedural Toradol, 30mg IV
- Foley catheter placement
  - Removed post-procedure if not catheter dependent

PAE Procedure

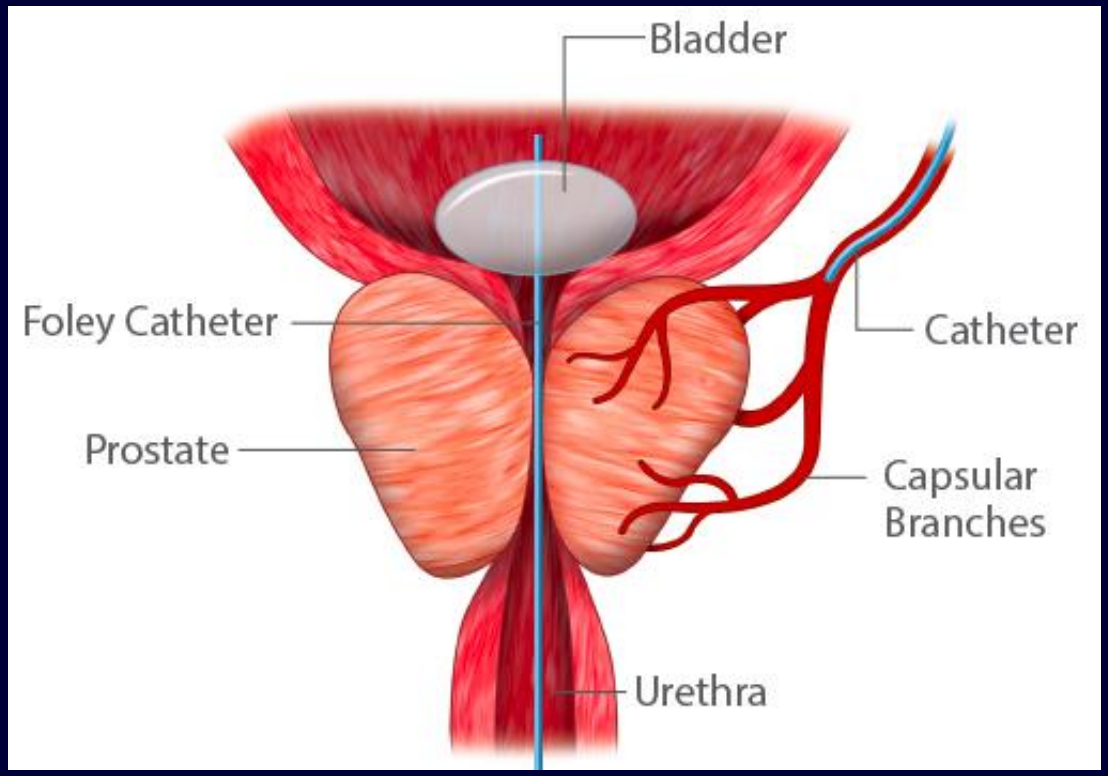
Vascular access





PAE Procedure

Super-selective arterial catheterization



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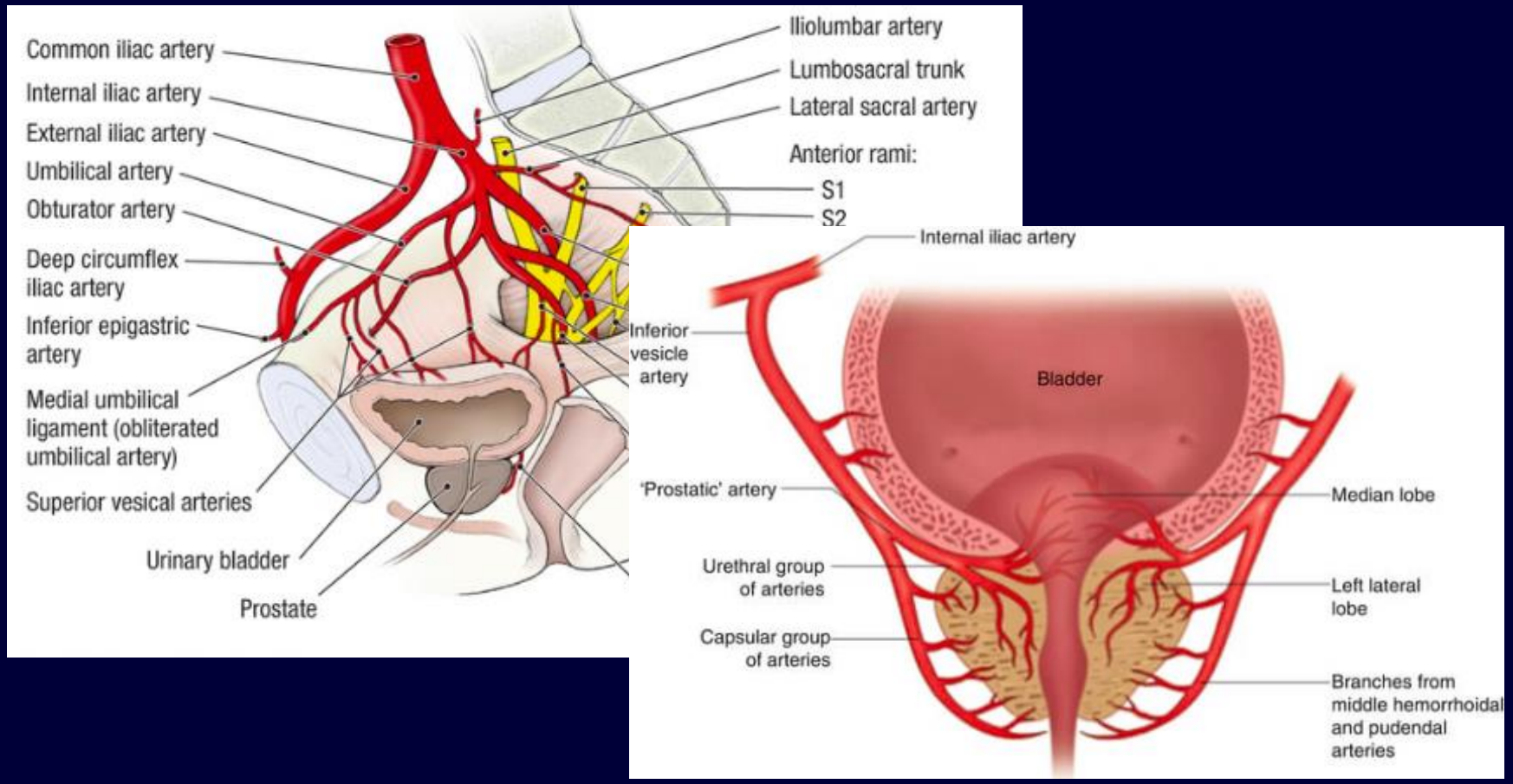

PAE Procedure

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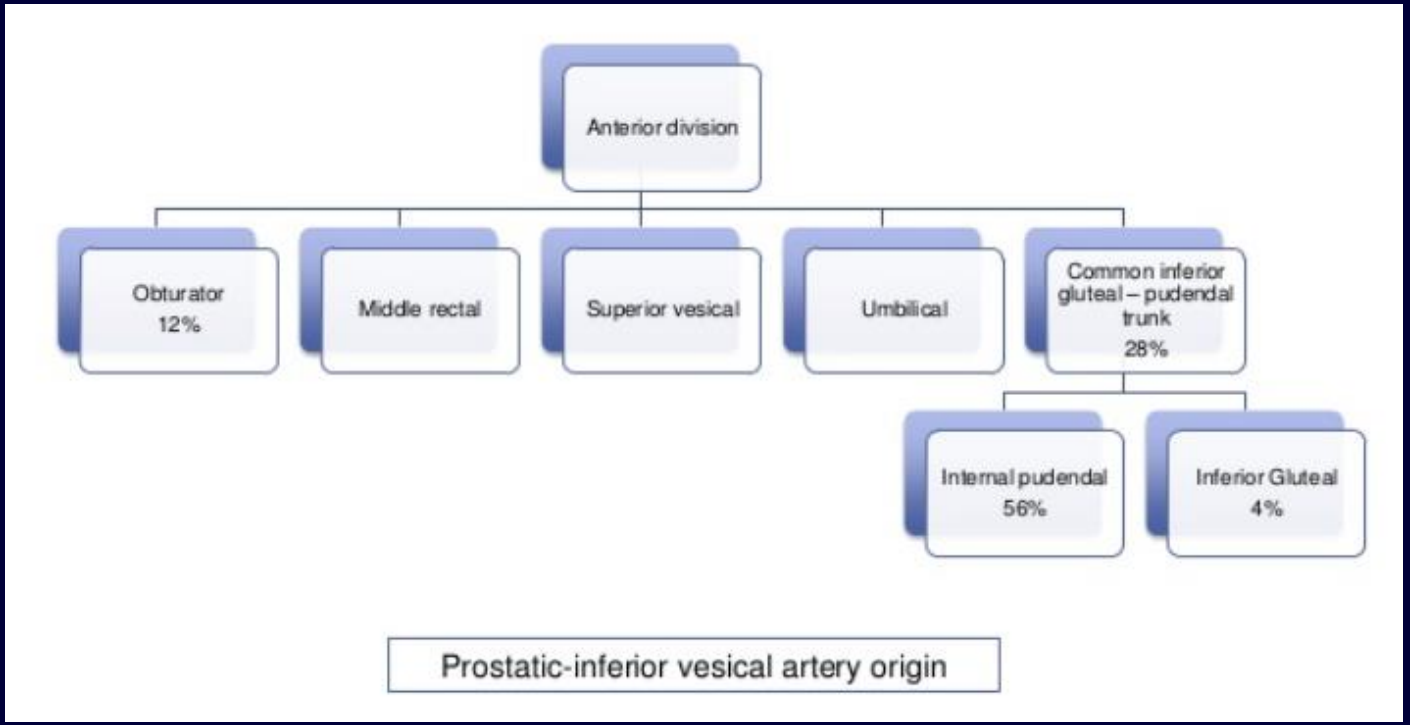
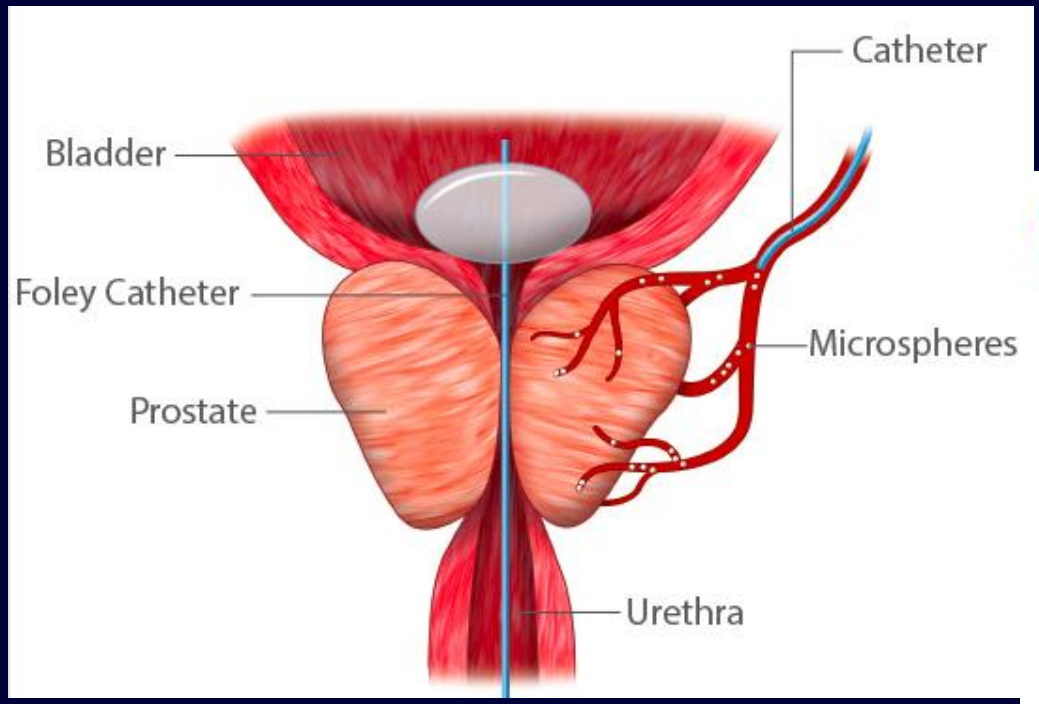
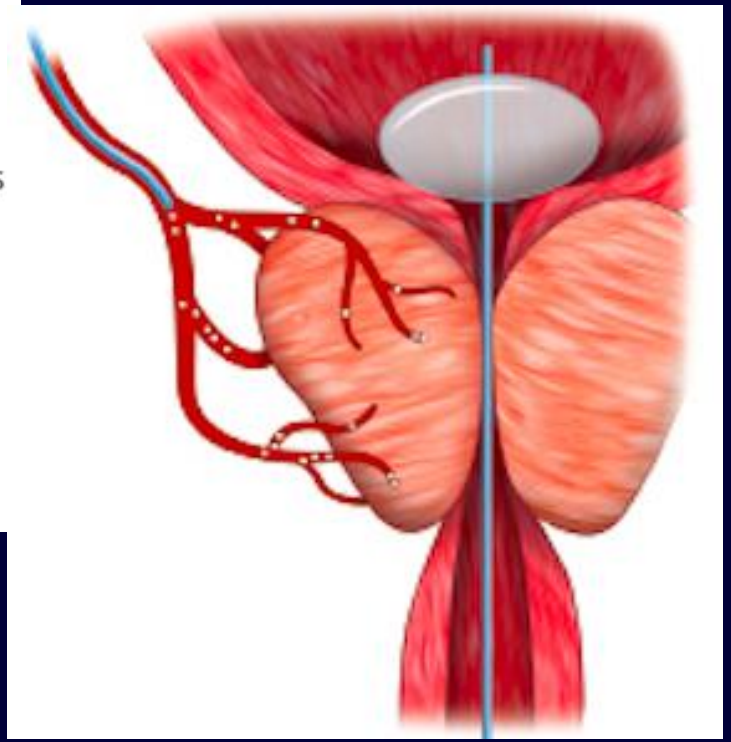


Complex pelvic arterial anatomy & collateral arterial arcades supplying bladder, rectum and penis

PAE Procedure

Particle embolization +/- coil embolization





PAE Procedure

Emboshperes®

Emboshperes® microspheres composed of trisacryl monomer and porcine gelatin

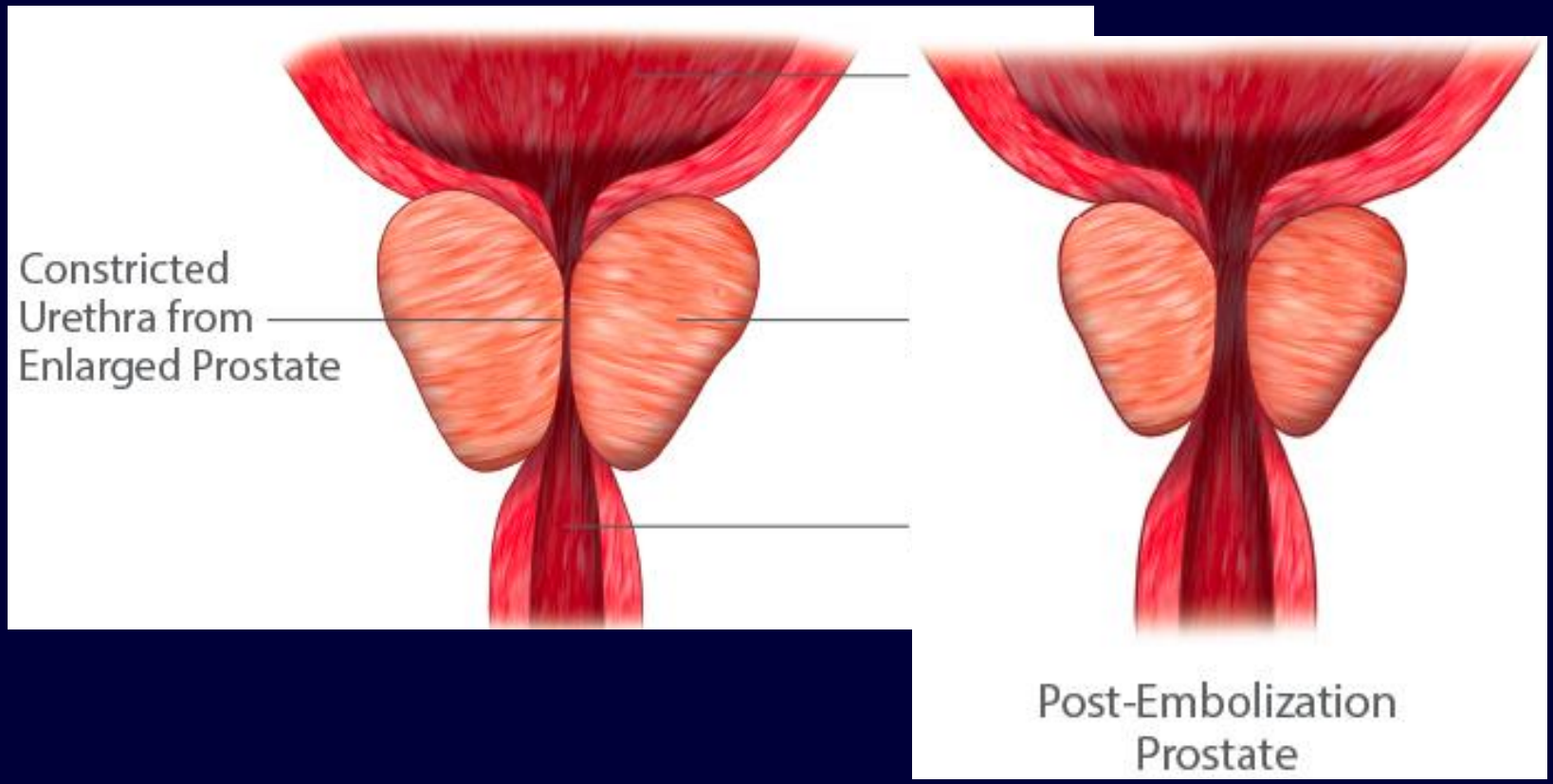
Highly consistent sphere size

Reliability of vascular occlusion level – Stop blood flow at level of pre-capillary arterioles

Smooth hydrophilic surface

PAE Procedure

Procedural outcome



PAE Procedure

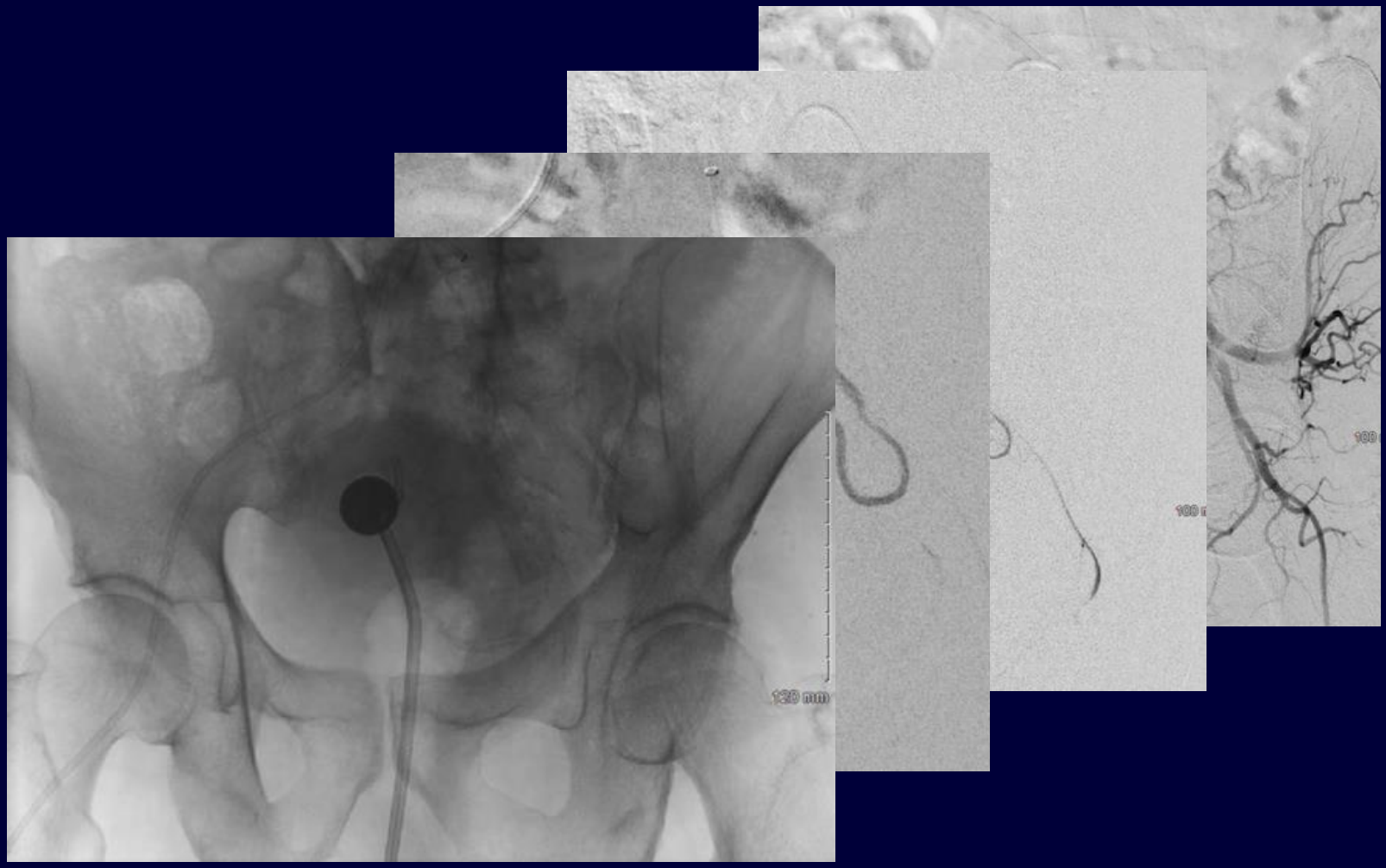
Post-procedural care:

- Post-PAE Syndrome x 3-5 days
  - Pelvic burning
  - Dysuria
  - Increased urinary frequency
- Pharmacologic management
  - Cipro BID for 7 days
  - Medrol DosePak
  - Motrin prn
  - Pyridium prn

Patient Example #1

90 yo M with h/o hematuria and multiple prior episodes of urinary retention; IPSS 30 and QoL 6

Patient Example #1



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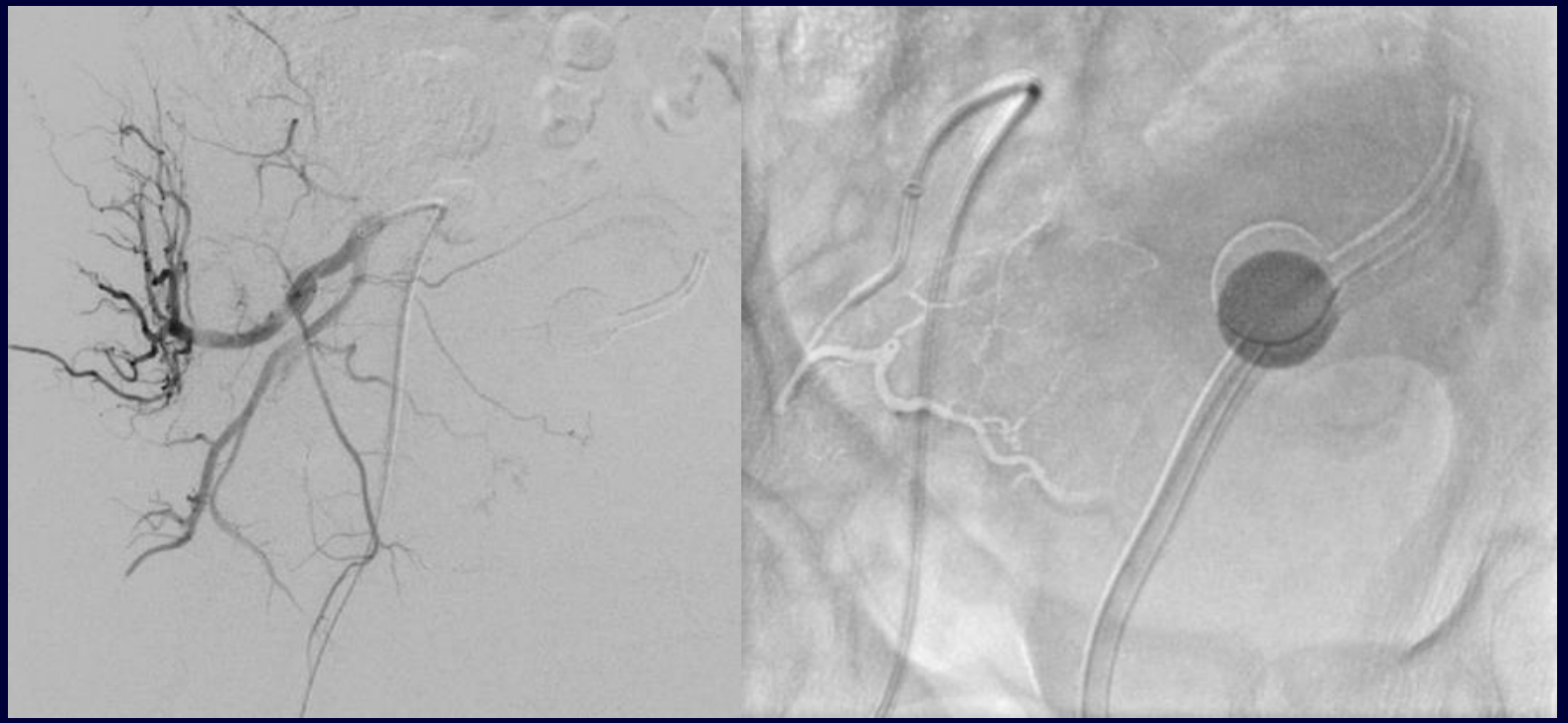

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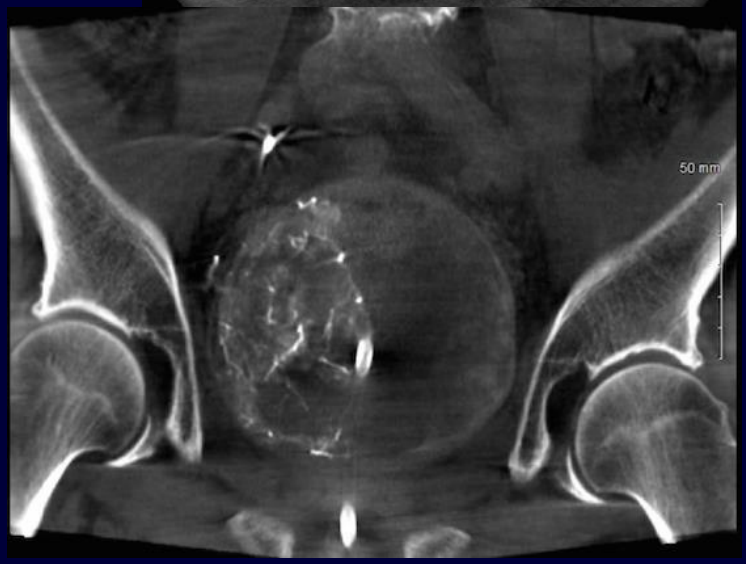
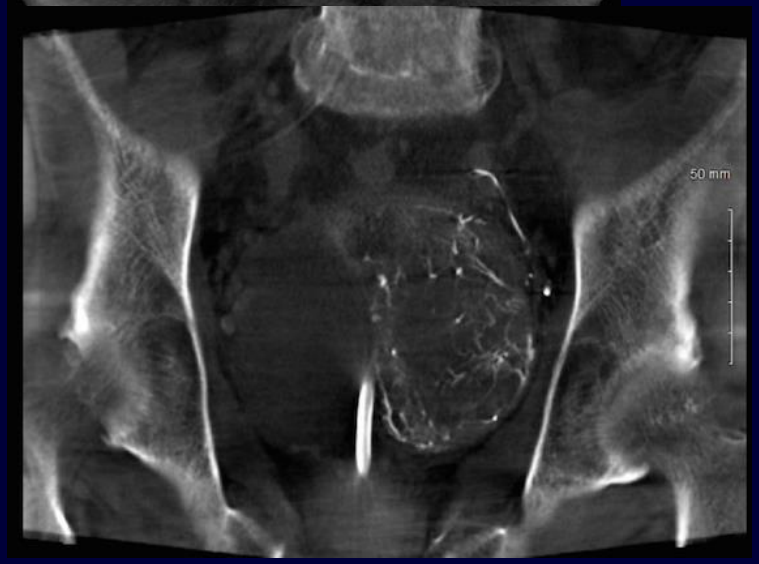
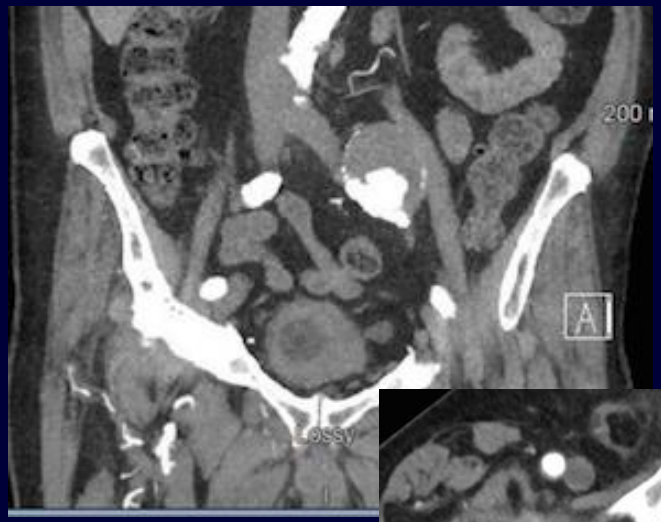
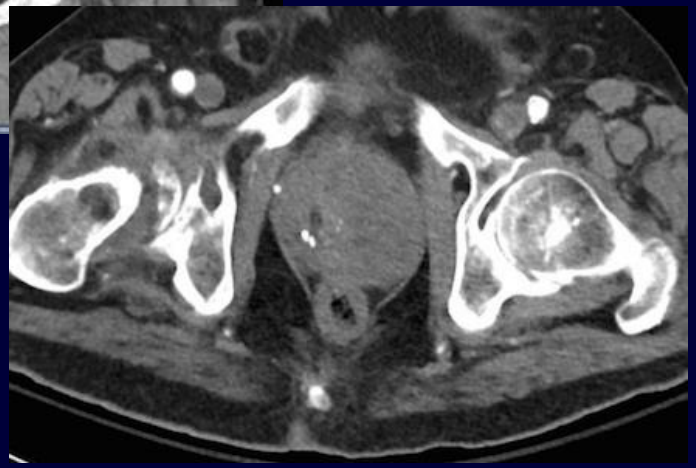




Patient Example #2

84 yo M in acute urinary retention and with a left common iliac artery aneurysm; 147 mL gland





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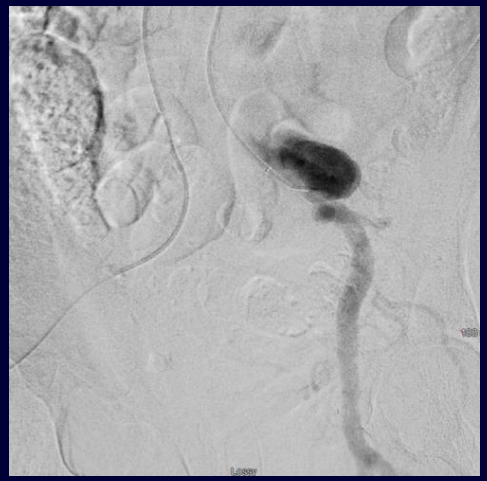
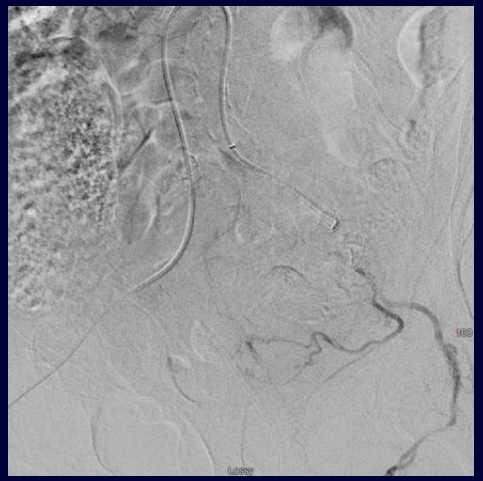
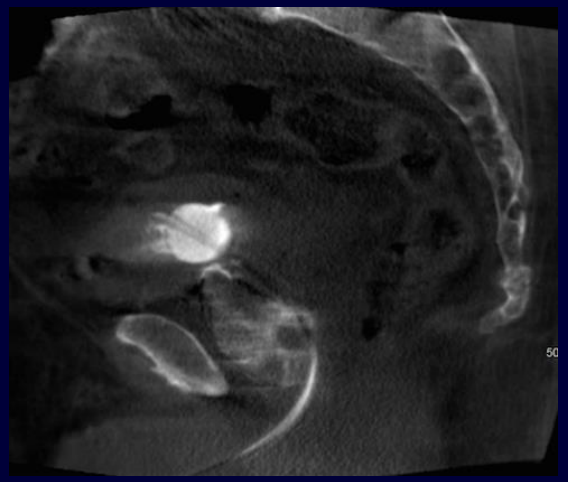
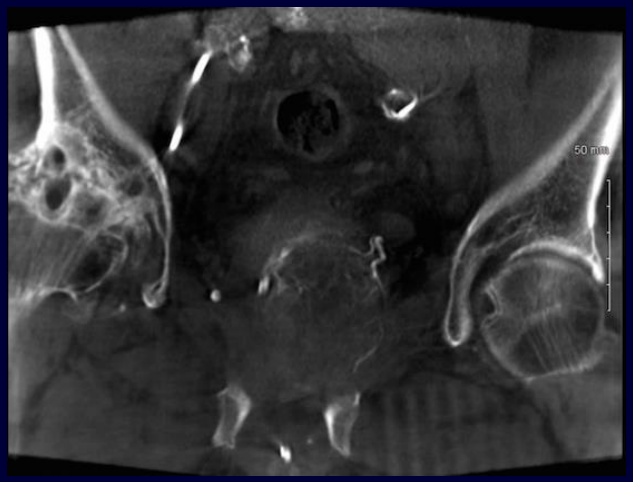
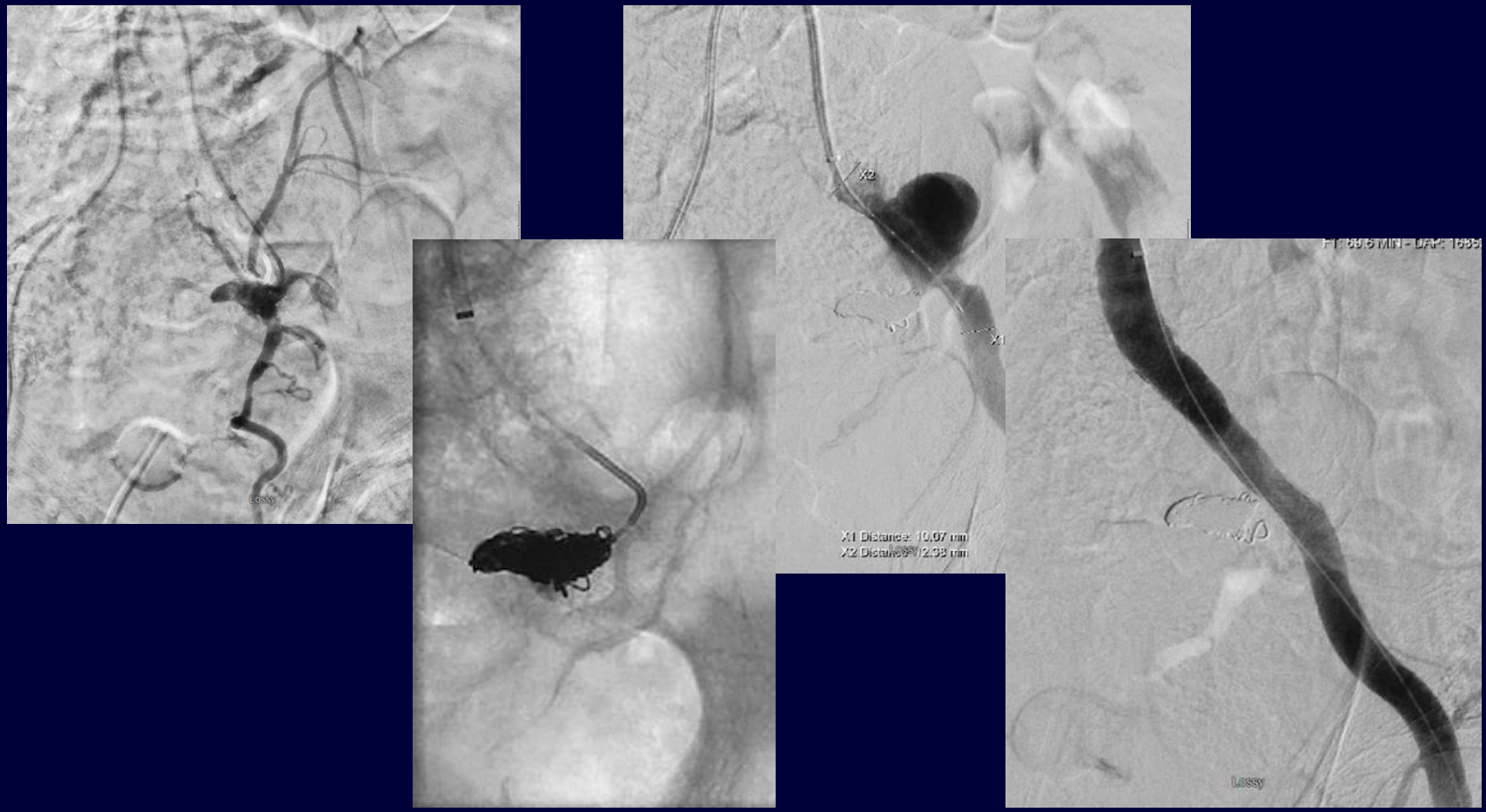




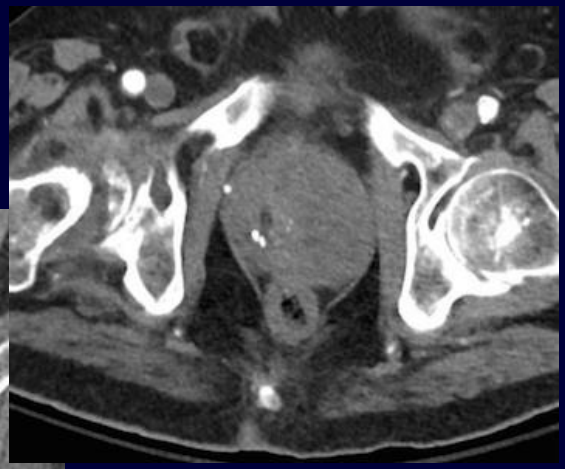




Patient Example #2



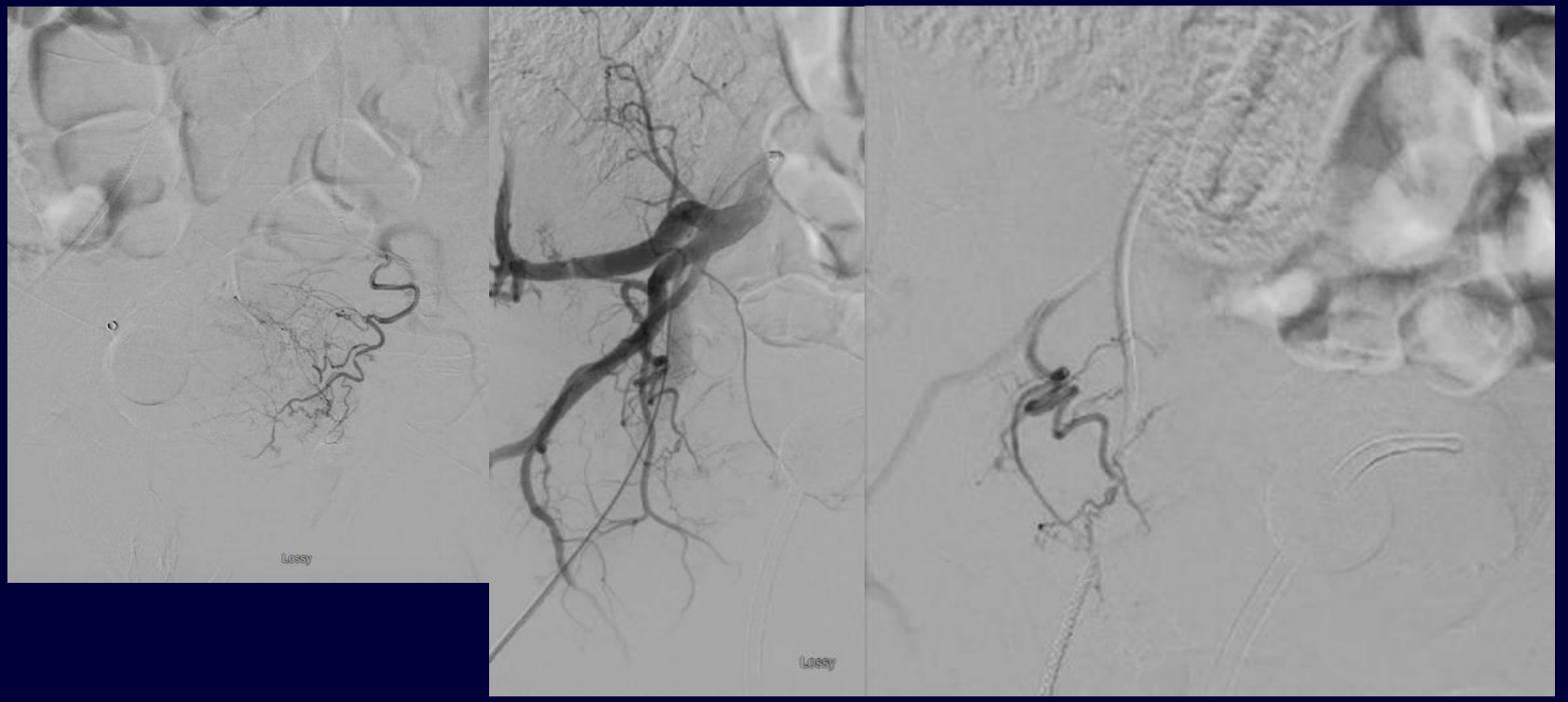
Patient Example #2



In 5 weeks,
147 mL to 102 mL

Patient Example #3

91 yo M with h/o urinary retention due to BPH; IPSS 27



Initial gland volume 221 mL, at approx 3 months 120 mL

Clinical Outcomes

Short- to Midterm Safety and Efficacy of Prostatic Artery Embolization: A Systematic Review

Ziga Cizman, MD, MPH, Ari Isaacson, MD, and Charles Burke, MD

http://dx.doi.org/10.1016/j.jvir.2016.04.015

ABSTRACT

Purpose: To review the available safety and efficacy data for prostatic artery embolization (PAE) in the treatment of benign prostatic hyperplasia (BPH).

Materials and Methods: PubMed was searched for publications that included PAE for the treatment of BPH through May 2015. Two independent reviewers determined the appropriateness for inclusion of each article and compiled data by using pooled weighted means and standard deviations.

Results: The literature search identified 161 articles, of which 7 studies, with a total of 562 patients, met all inclusion/exclusion criteria. PAEs were performed bilaterally in 85% of patients, unilaterally in 12%, and unsuccessfully in 3%. International Prostate Symptom Score decreased from 24.51 ± 6.12 at baseline to 10.42 ± 5.39 at 6 months. Quality of life score decreased from 4.76 ± 0.98 at baseline to 2.51 ± 1.13 at 6 months. Peak urinary flow rate increased from 8.41 mL/s ± 2.63 at baseline to 15.44 mL/s ± 5.64 at 6 months. Postvoid residual measurement decreased from 105.94 mL ± 76.77 at baseline to 39.57 mL ± 15 at 6 months. Prostate-specific antigen level decreased from 4.79 ng/mL ± 5.42 at baseline to 3.16 ng/mL ± 1.5 at 6 months. None of these parameters showed clinically significant changes from 6 months to 12 months. Total prostate volume decreased from 96.56 cm3 ± 35.47 at baseline to 46.73 cm3 ± 20.51 at 12 months. There were 200 minor complications and 1 major complication.

Conclusions: PAE improves lower urinary tract symptoms caused by BPH, with a favorable short- to midterm safety profile.

Clinical Outcomes

Patient Outcomes:

- Technical success
  - Bilateral embolization performed in 85% pts
  - Unilateral embolization performed in 12% pts
  - Inability to embolize in 3% pts
    - Atherosclerotic disease, vascular occlusion/tortuosity
  - Technical failure rate of 15%
- Post-procedure admission
  - Up to 84% pts discharged within 24 hrs of procedure
  - Average length of stay if admitted, 3 days

Clinical Outcomes

Complications According to SIR Criteria	
Complication	**Incidence**
Grade A	
Pain	46 (8.19)
Hematuria	25 (4.45)
Hematospermia	23 (4.09)
Urethral burning	19 (3.38)
Rectal bleeding	17 (3.02)
UTI*	5 (0.89)
Balanitis	4 (0.71)
Hematoma	4 (0.71)
Diarrhea	3 (0.53)
Dissection	1 (0.18)
Grade B	
Acute urinary retention	51 (9.07)
Nontarget embolization	1 (0.18)
UTI	1 (0.18)
Grade C	0
Grade D	
Nontarget embolization	1 (0.18)
Grade E	0
Grade F	0

Note–Values in parentheses are percentages.
SIR = Society of Interventional Radiology; UTI = urinary tract infection.
* Calculation excludes preexisting UTIs (confirmed by culture) found in 14 of 19 patients in the study of Pisco et al (11).

Blood loss requiring transfusion, bladder incontinence and erectile dysfunction NOT reported with PAE

Clinical Outcomes

Clinical results:

- Clinical success in 88% pts
  - 12% clinical failure
    - LUTS medical therapy failure rate, 7.3-17.1%
    - TURP repeat intervention rate at 5 yrs, 8.9-9.7%
    - Equivalent repeat intervention rate at 1 yr for transurethral vaporization, laser resection and thermal ablation

Clinical Outcomes

Clinical results:

- 6 months post PAE
  - Mean IPSS decreased from 25±6 → 10±5
    - At 12 months, 59% reduction
  - QOL Score decreased from 5±1 →2.5±1
    - At 12 months, 56% reduction
  - Qmax increased from 8±3 → 15±6 mL/s
    - At 12 months, 91% increase
  - PVR decreased from 106±77 → 40±15 mL
  - TPV decreased from 100±35 → 63±28 cm^3
    - At 12 months, down to 47±21 cm^3
  - No change in IIEF-5 score
    - At 12 months, no change

No reported ejaculatory dysfunction, even at 12 months

Clinical Outcomes

Long-term results:

- 6 months post PAE
  - Mean IPSS decreased from 25±6 → 10±5
    - At 12 months, 59% reduction
  - QOL Score decreased from 5±1 →2.5±1
    - At 12 months, 56% reduction
  - Qmax increased from 8±3 → 15±6 mL/s
    - At 12 months, 91% increase
  - PVR decreased from 106±77 → 40±15 mL
  - TPV decreased from 100±35 → 63±28 cm^3
    - At 12 months, down to 47±21 cm^3
  - No change in IIEF-5 score
    - At 12 months, no change

Clinical Outcomes

Pisco et al 2016:

- Largest cohort of pts, 630, with at least 6 month f/u
  - Prostate volume and PVR improved significantly (P<0.0001)
  - Clinical success
    - IPSS ≤ 15 or 25% decrease
    - QOL Score ≤ 3 or decease of at least 1 point
      - At 3, 6, 12, 24, 48 and 78 months, clinical success rates of 90%, 88%, 85%, 82%, 81% and 76%

F/U Duration	Mean IPSS Improvement	QOL Improvement	Qmax Increase
Short-term (12 months)	-13.7 ± 7.2	-1.9 ± 1.2	3.1ml/s ± 5.8
Medium-term (1-3 years)	-14.5 ± 7.4	-2.0 ± 1.2	4.1ml/s ± 11.3
Long-term (3-6.5 years)	-16.9 ± 8.7	-1.7 ± 1.5	8.0ml/s ± 4.8

Clinical Outcomes

Kuang et al Meta-Analysis 2017:

- 788 patients from literature
- Significant improvement in multiple parameters
  - Prostate volume
  - PVR
  - Qmax
    - Mean 8.3mL/s to 14.3, 15.9 and 16.9 at 6, 12 and 24 months
  - IPSS
    - Mean 23.8 to 10.9, 9.3, and 8.9 at 6, 12 and 24 months ($P<0.001$)
  - QoL
    - Mean 4.6 to 2.5, 2.1 , and 2.4 at 6, 12 and 24 months ($P<0.001$)

Clinical Outcomes

Gao et al RCT of PAE vs TURP:

- 114 pts, PAE (n=57) and TURP (n=57)
- TURP
  - Significantly better improvement in IPSS, QoL, Qmax and PVR at 1 and 3 months
  - Prostatic tissue must undergo necrosis and remodeling s/p PAE
- At 6 months, treatments equivalent
- Remain equivalent at 12 and 24 months

Clinical Outcomes

Prostate artery embolization may improve erectile function with no deleterious effect on ejaculation: a retrospective review of 53 patients

S Bhatia, S Tewari, C Gomez, B Kava, V Sinha and G Narayanan

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- TURP and Photoselective vaporization
  - Adverse sexual effects
    - Retrograde ejaculation or erectile dysfuction
- PAE successfully performed in 50/53 pts
  - SHIM Score at baseline, 1 and 3 months – 13.3., 13.5 and 16.2
  - At 3 months, 64% had improvement, 16% no change and 20% negative change
    - Change at 3 months, average +2.9, statistically significant
    - No new onset retrograde ejaculation

Clinical Outcomes

Sexual Health Inventory For Men (SHIM)

Instructions

Each question has 5 possible responses. Circle the number that best describes your own situation.
Select only 1 answer for each question.

Over the past 6 months:

1. How do you rate your confidence that you could keep an erection?

1	2	3	4	5
Very low	Low	Moderate	High	Very high

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?

1	2	3	4	5
Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

1	2	3	4	5
Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

1	2	3	4	5
Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult

5. When you attempted sexual intercourse, how often was it satisfactory for you?

1	2	3	4	5
Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always

22-25	No ED
17-21	Mild ED
12-16	Mild-to-moderate ED
8-11	Moderate ED
5-7	Severe ED

Clinical Outcomes

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- Mean IPSS
  - Baseline, 1 and 3 months – 25.8, 8.8 and 7.4
- QoL
  - Baseline, 1 and 3 months – 4.9, 1.8 and 1.3
- PV
  - Baseline and 3 months – 110g and 71g
- Complications
  - Urosepsis tx with IV antibiotics

PAE associated with statistically significant improvement in erectile function

Take-Home Points

- BPH is a common condition amongst aging men
- Hematuria and LUTS due to BPH may be successfully treated with PAE
- PAE is a safe, minimally invasive treatment option
  - Acceptable side effect profile
  - No resultant erectile dysfunction
  - Enables patients to tolerate anticoagulation
- Future applications are promising
  - Possible chemotherapy/radiotherapy-augmented embolization in treatment of prostate cancer

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Thank You

Special thanks to my Interventional Technologists & Nursing Staff