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# Use of Laser Light to Treat Benign Prostatic Hyperplasia and Prostate Cancer


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Study sponsored by StebaBiotech, Paris, France


**No conflict of interest to declare**


Conference on Laser, Omics and Photonics
Philadelphia, Sept. 8th 2014

# Outline

- The prostate, benign prostatic hyperplasia (BPH) and prostate cancer (PCa)

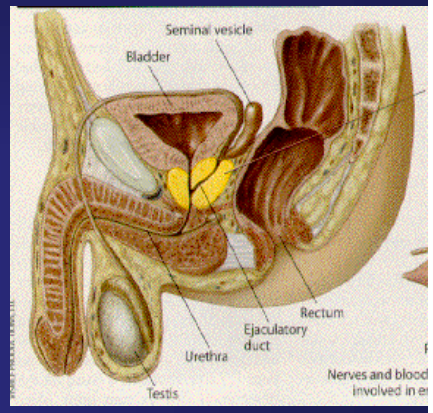
- BPH: Incidence, symptoms, treatments
- Photodynamic therapy (PDT)
- PDT for BPH: Development of an endoscopic procedure

- PCa: Incidence, symptoms and treatments
- PDT for PCa: first clinical trial and optimization of new procedure

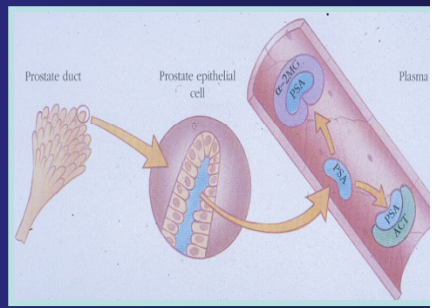
# The prostate

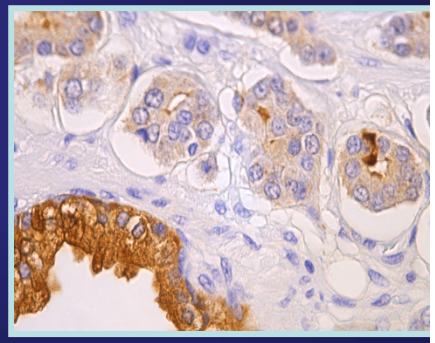
- Integral organ of the male uro-genital tract

- Secretory function with products poured in semen at ejaculation, including the protease called Prostatic Specific Antigen (PSA) to allow sperm coagulum to liquefy
- PSA is released in the blood of men with prostatic proliferative diseases




- Tissue constituants: i) glands with three epithelial cell Subtypes, the luminal characteristic of prostate secrete products into the semen;
ii) surrounding stroma with collagen & smooth muscle fibers, blood vessels, inflammatory cells



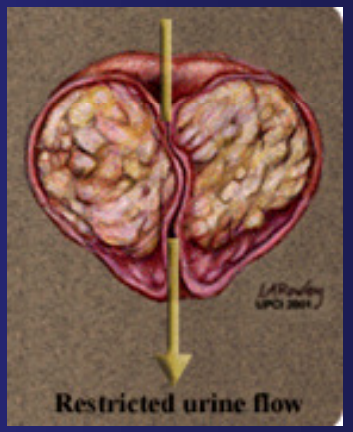
- Postnatal growth at puberty 1-2g to 20g by age of 20y
  - slow rate during adulthood (by 50-60y: 40-50g)
  - grow again with benign nodules in transition zone or peri-urethral leading to BPH (benign prostatic hyperplasia)
  - parallel development of prostate cancer (**PCa**) in periphery

# BPH: Incidence, symptoms and therapies

- Incidence
  - almost all aging men (> 50 year old) but not all require therapy (Tx)
  - exact causes: unknown beside aging
  - risk factors: androgens (male hormones) invoked

- Lower Urinary Tract Symptoms (LUTS)
  - most common: difficulty to urinate, frequency, reduced flow and volume
  - severe: urinary retention *vs.* risk of renal damages

- Tx according to quality of life, severity of LUTS
  - pharmacologic (drugs)
    - α-adrenergic to inhibit nerve endings and relax smooth muscle contraction
    - 5α-reductase inhibitors enzyme converting Testosterone to its metabolite DHT which is more potent on growth
    - combination is best
  - surgical: resection large volume prostates, including with lasers

# BPH: problems

- effects not definitive, regrowth vs. removal of more tissues
- patient compliance to drugs
- side-effects of surgery

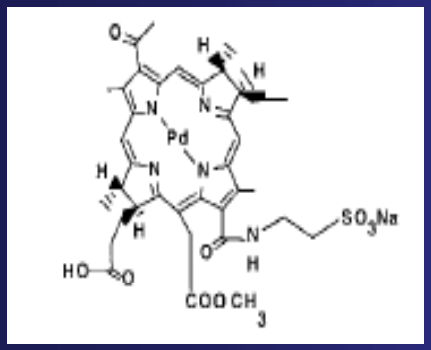
Room to introduce new minimally invasive modalities for small volume prostates and moderate LUTS

# Principle of Photodynamic Therapy (PDT)

Photosensitizers *i.v.* + **Light (Laser diode)**

**A 753nm**

**Fiber diffuser in target organ (prostate)**




WST11: Bacteriochlorophyll*

Activated photosensitizers

Tissue-based

Vascular (WST11)

**ROS**

Cell death (Necrosis)

*WST09 had been optimized for PCa when WST11 (highly soluble) was discovered

# Endoscopic PDT with WST11 for BPH:

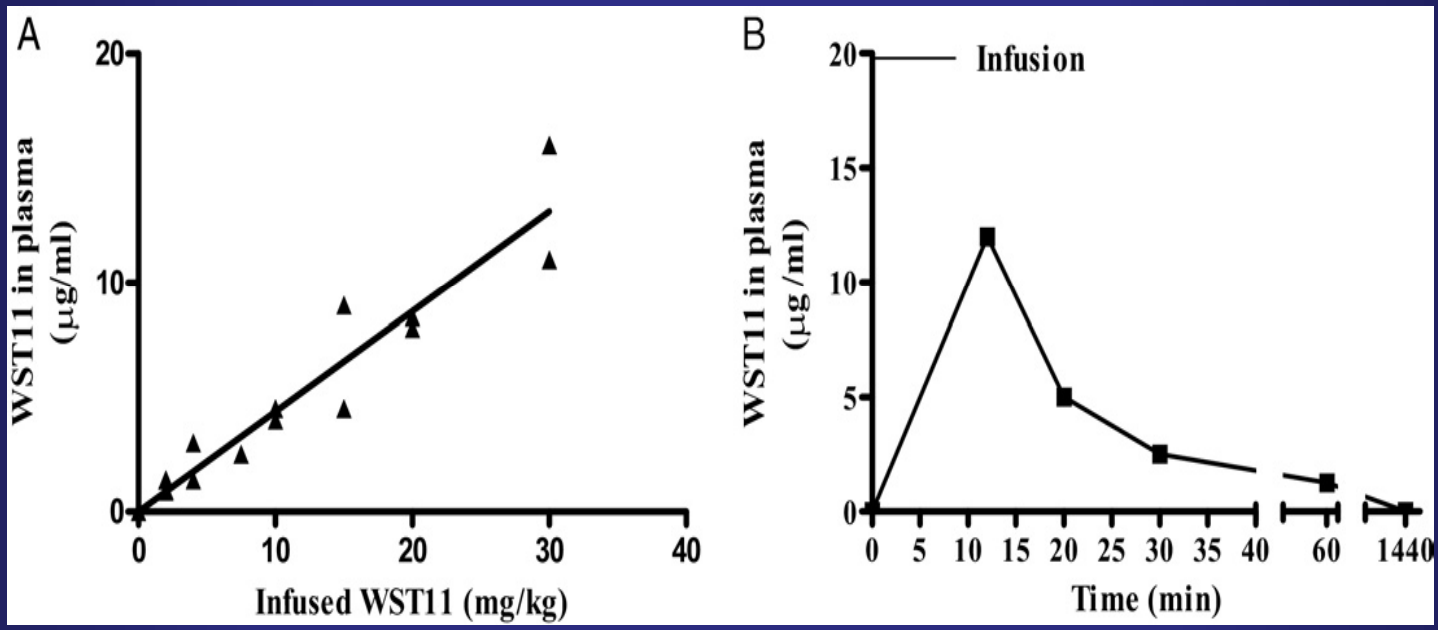
## Could this be a mean to reduce LUTS?

*First time study with no known parameters

Chevalier et al, J Urol. 190: 1946-53, Nov 2013

# Pharmacokinetics

The canine species represents a model of choice for studies on the prostate given that dogs spontaneously develop BPH and PCa with age



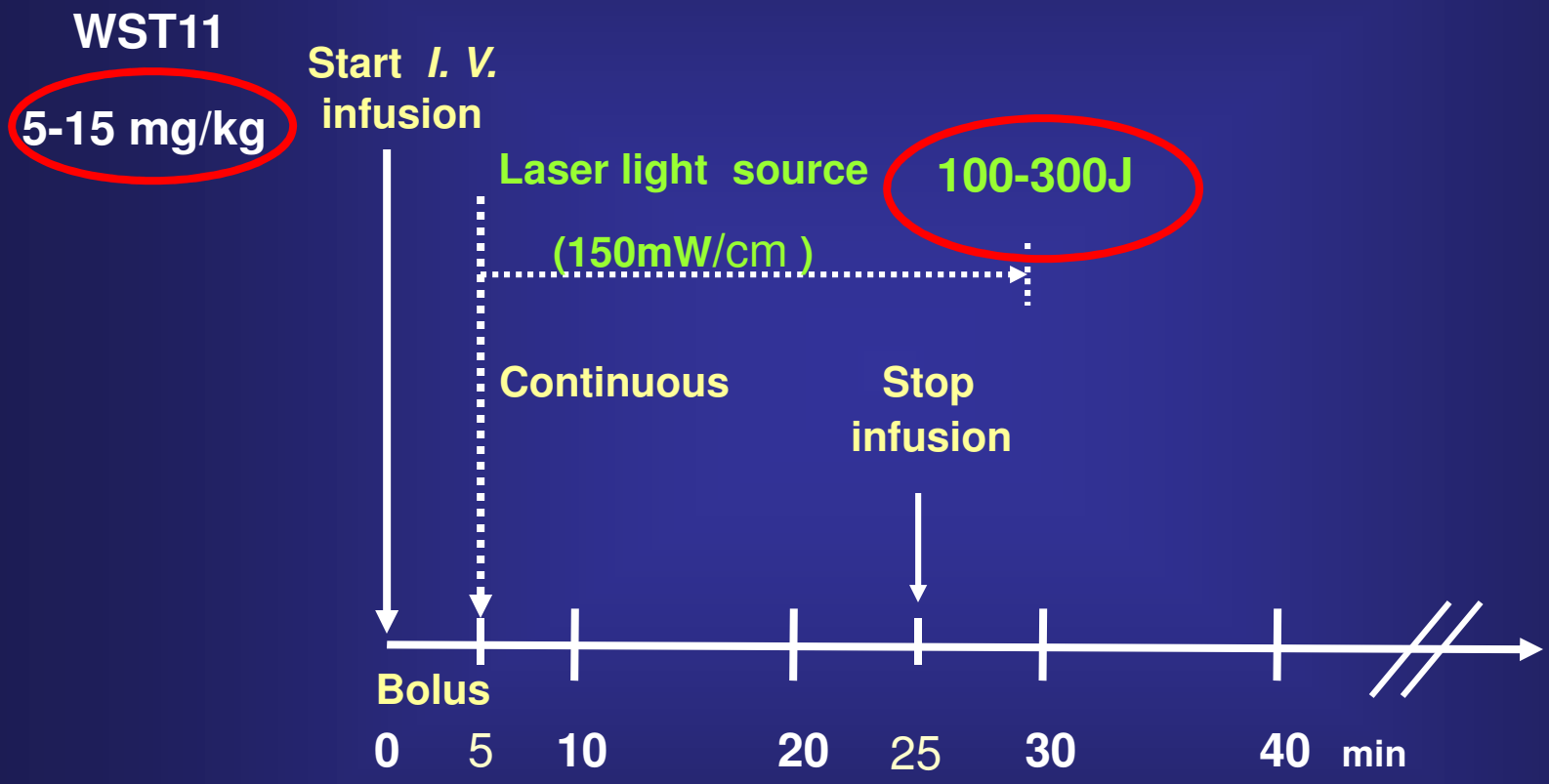

Cmax *vs.* 2 to 30 mg/kg WST11
(r2 = 0.90)

Representative dog
WST11 at 7.5 mg/kg
Cmax by ~10 to 11 minutes

Short half-life, advantageous to minimize skin toxicity to sun exposure

# Procedure per se

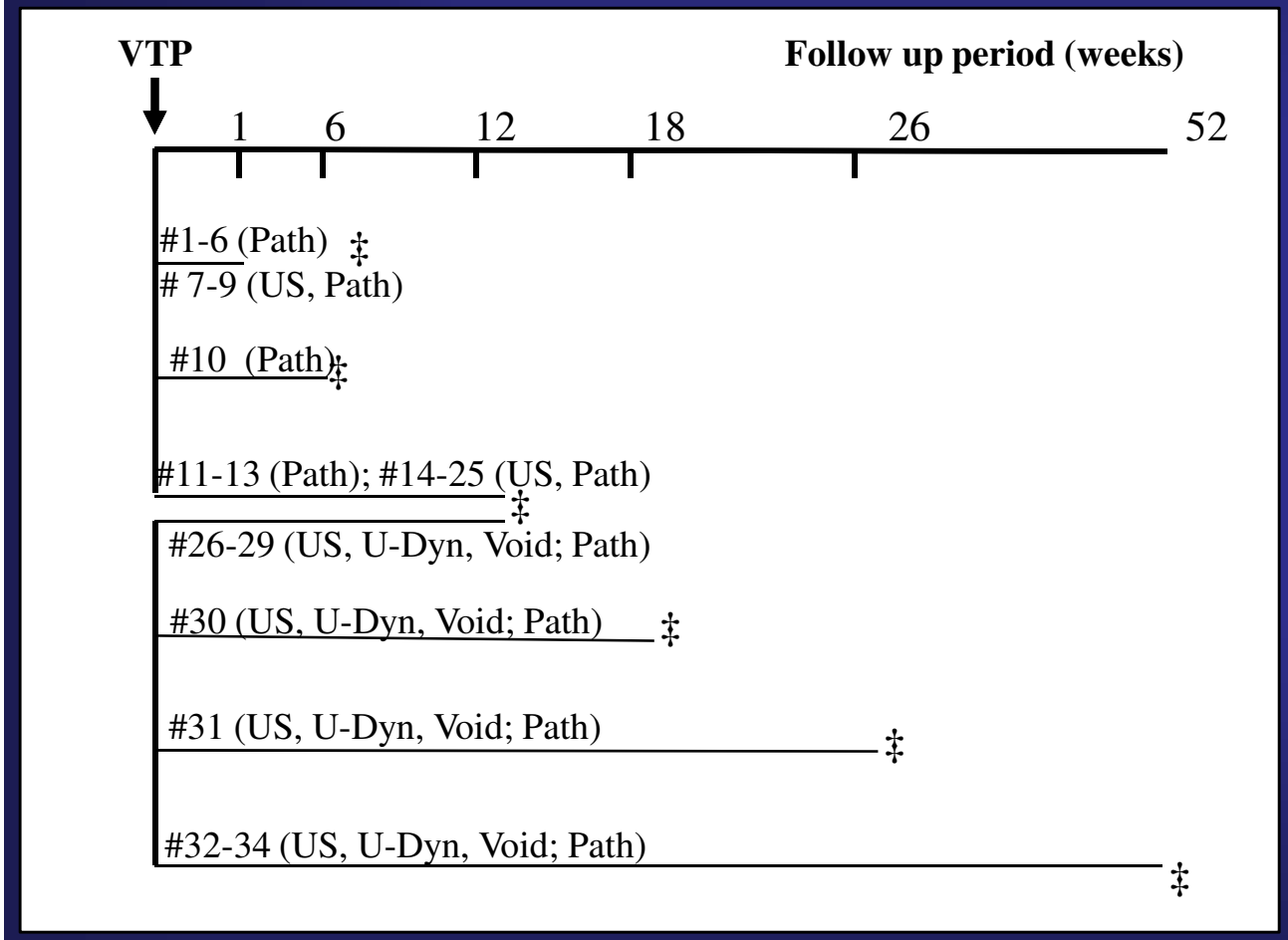
Cystoscopy (flexible endoscope) to position a fiber (diffuser: 1cm) in the the prostatic urethra




- ✓ Blood pressure monitoring
- ✓ Blood sampling for pharmaco-kinetics, biochemical and hematological tests
- ✓ Clinical follow up *vs.* endpoints from 1wk to 1 year in 3 dogs (aged mongrel; 25-40kg)

# Efficacy

*34 dogs with 2 light and 2 WST11 controls*




Pre and post-PDT over time:

- ✓Ultra-sound (US)
- ✓ Video of provoked voiding (Void)
- ✓Urodynamics (U-Dyn)
- ✓ Histo-pathology (Path)

# Endoscopic PDT causes macoscopic hemorrhages

WST11: 15mg/kg
Light source (150mW/cm)
300J with a 1cm diffuser

At the1 wk endpoint:

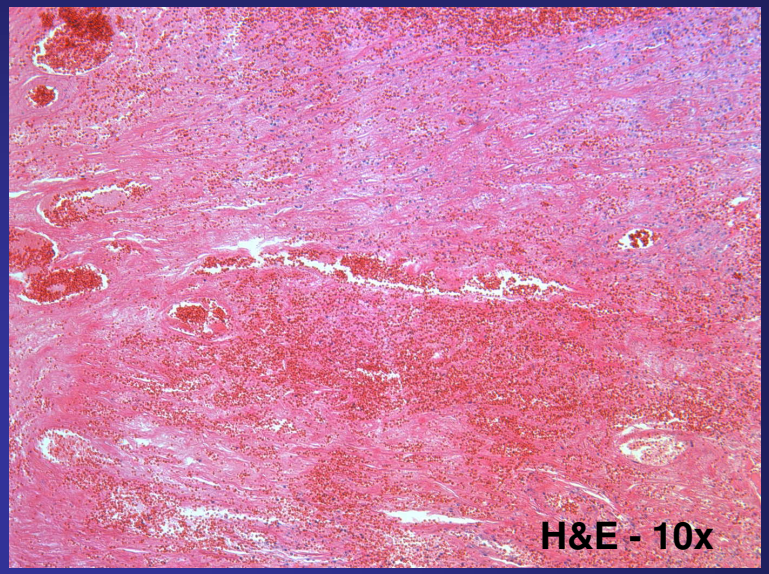
- Prostate fixed and sliced from base to apex (4mm thick)

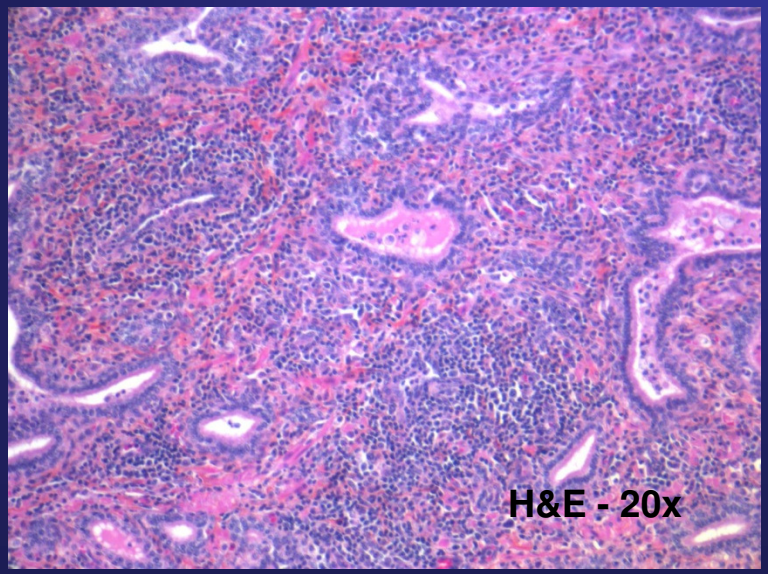
- Fixed and processed as whole Mounted paraffin (FFPE) blocks to see the urethra in the centre

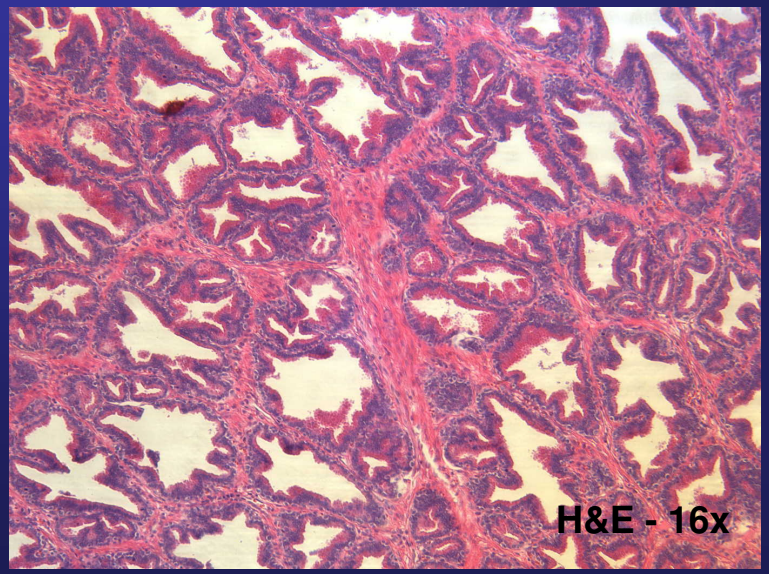
Visible hemorrhages surrounding the prostatic urethra

# Prostate hispathotology

WST11: 15mg/kg; Light energy: 300J & 1cm diffuser; Analysis at 1wk post-PDT

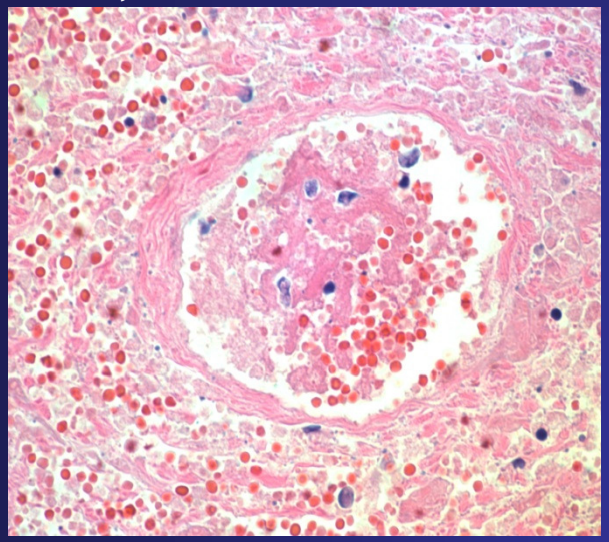



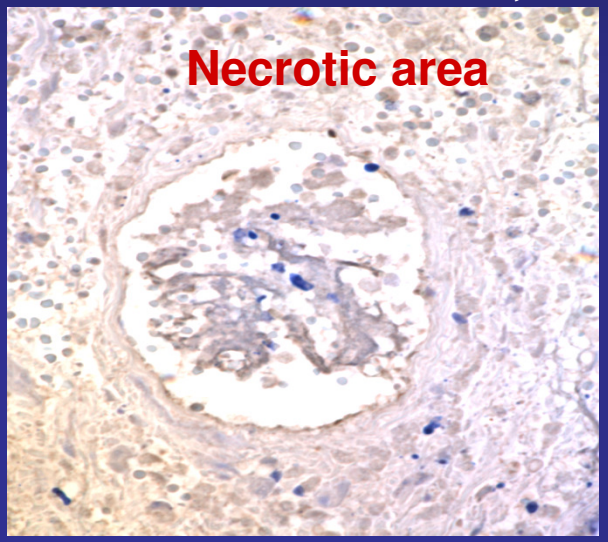
# PDT-induces damages in blood vessels: Vascular Targeted Therapy (VTP)

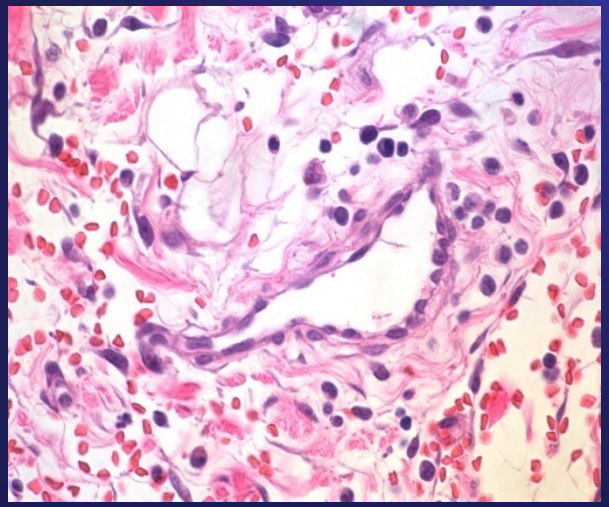
**WST11: 15mg/kg ; Light: 300J/cm; Analysis at 1wk**

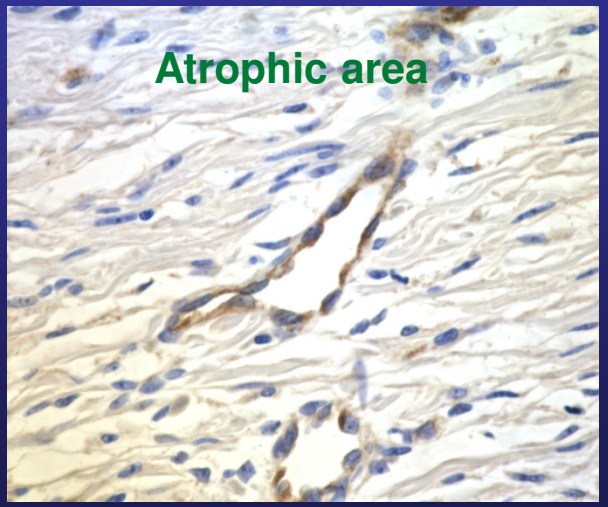
**H&E, 64x**



**IHC Factor VIII, 64x**






Endothelial layer of blood vessels is lost only in necrotic area and not the surrounding atrophic area

Tissue disruption allows blood leakage

* Urethral sphincter is intact

# Efficacy: necrosis and atrophy

**Necrosis (morphometry)** **0** **0** **15** **7** **65** **121mm2**

*** Atrophy of glands & inflammation**

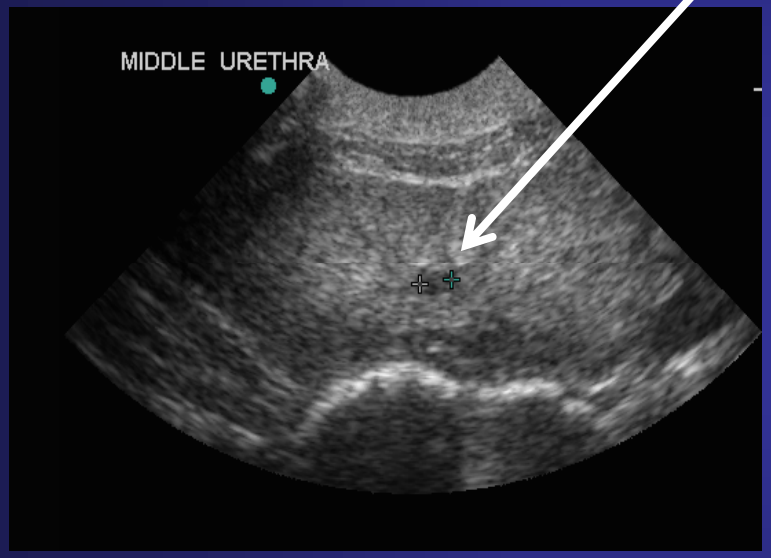
Mapping necrosis and atrophy on microscopic sections from all prostate blocks

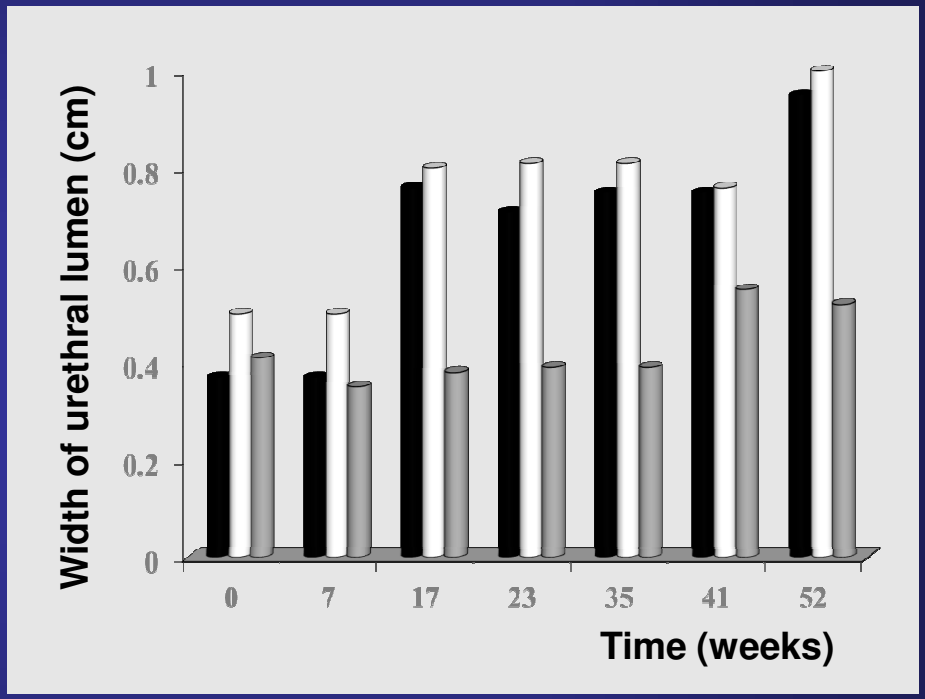
Morphometry allowed quantification of affected zone expressed by surface

# Measure of prostatic urethral diameter

Trans-abdominal ultra-sound imaging of prostate prior to and over-time post-PDT

Urethral width at base (cranial), middle, apex (caudal)

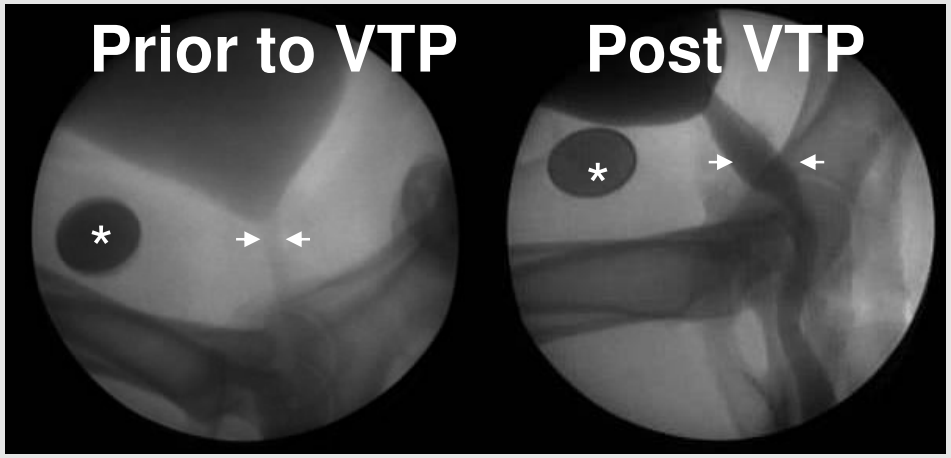


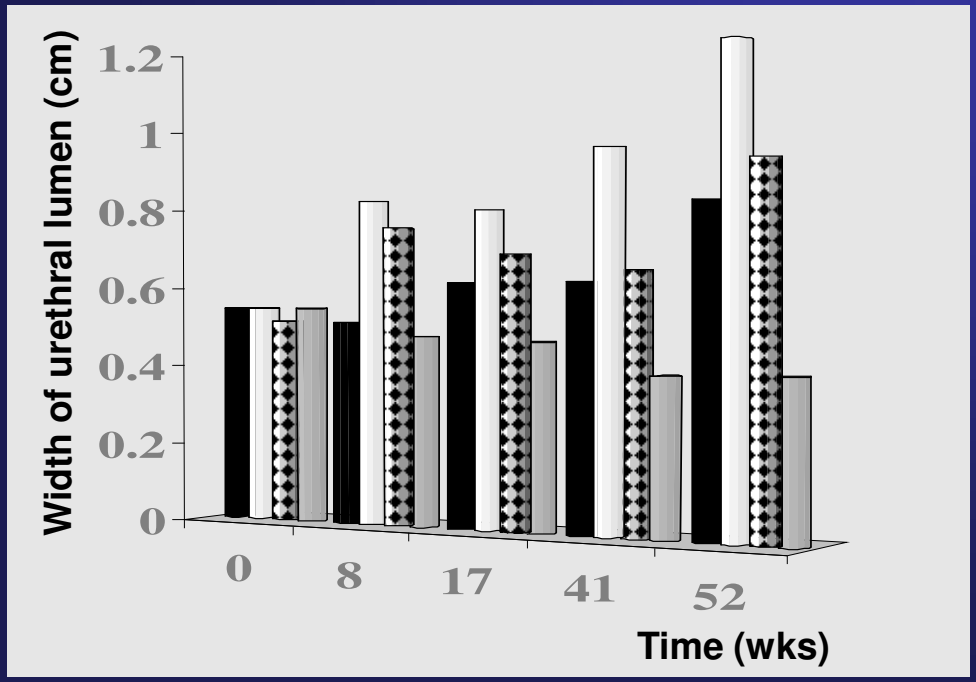




- Increased diameter at base and middle portions (*vs.* fiber positioning) between 7-17 wks (earliest seen at 6-9 wks) and continue to increase over time
- Values constant in all portions of urethra in control 2 dogs with laser light only and no WST11 as well as one without laser infused WST11
- Lesions exceed the 1cm diffuser length

# PDT-induced changes in urethral width at voiding

* Dime to correct for image distorsion




Bladder filled with saline + contrast until dripping

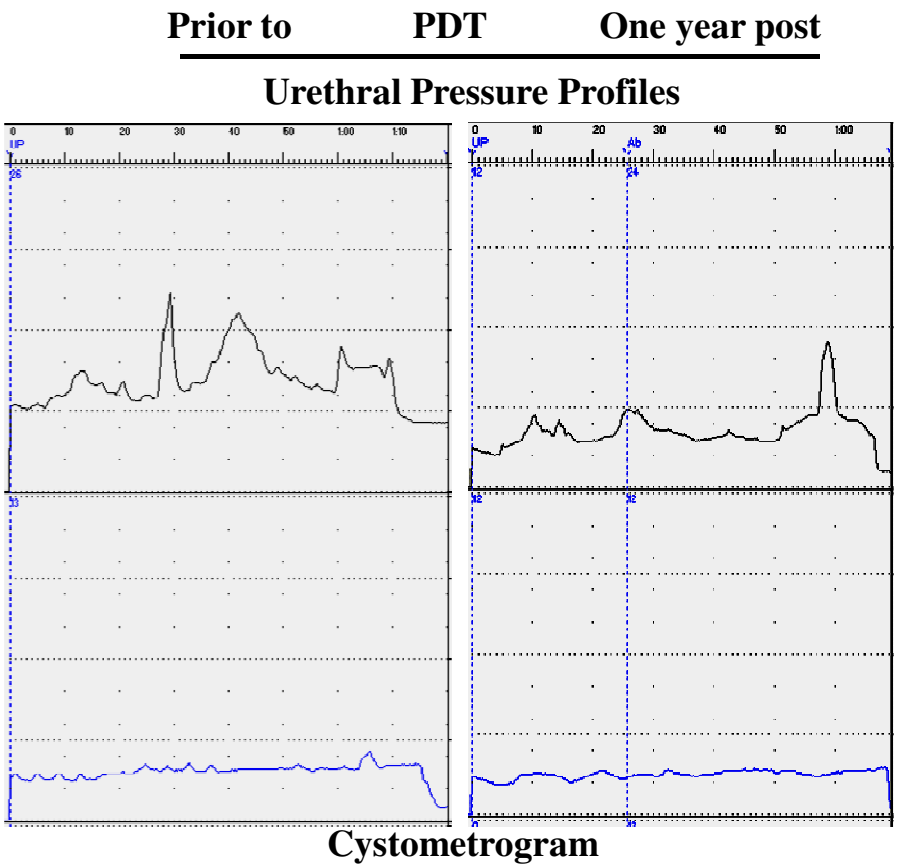
Press on abdomen to provoke voiding and record by video while doing fluoroscopy; repeat
3-5 times

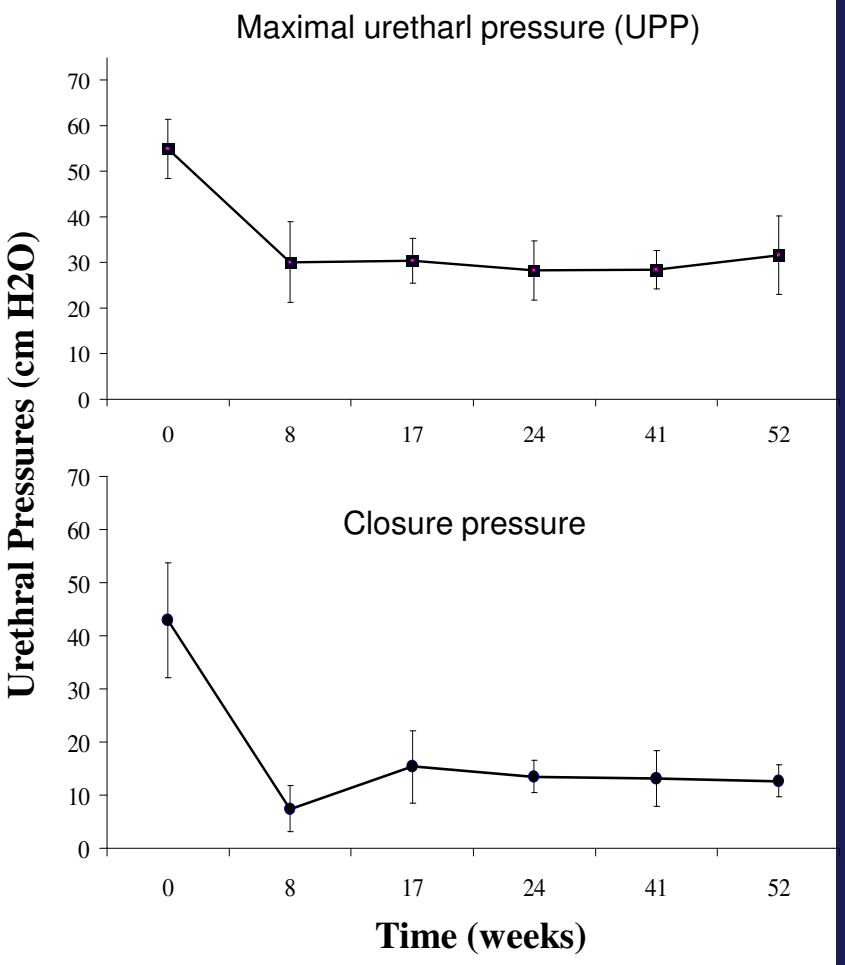
Images analysis: measures of urethral width at every 1 cm from bladder neck and over 4cm
prostate urethral length is ~3.0 cms, (n=34)

- Increase in urethral width noticed by 8wks and continued to increase over 1year
- Affected urethral portion is 2cm from bladder neck

# PDT-induced changes in urethral pressures

Special cathether to record pressure in urethra through computerized equipement

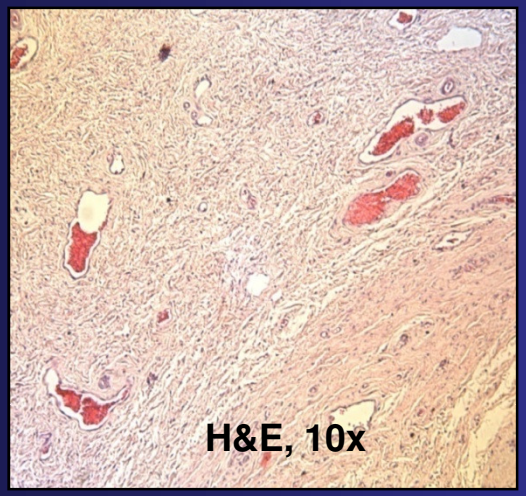


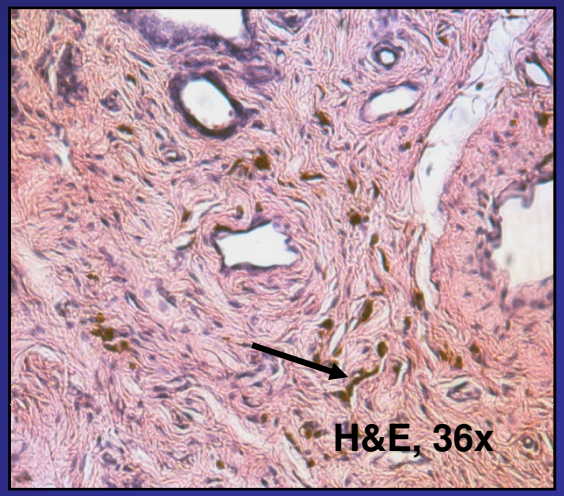

Lower pressure implies less resistance to void (*p< 0.01; group of 3 dogs)

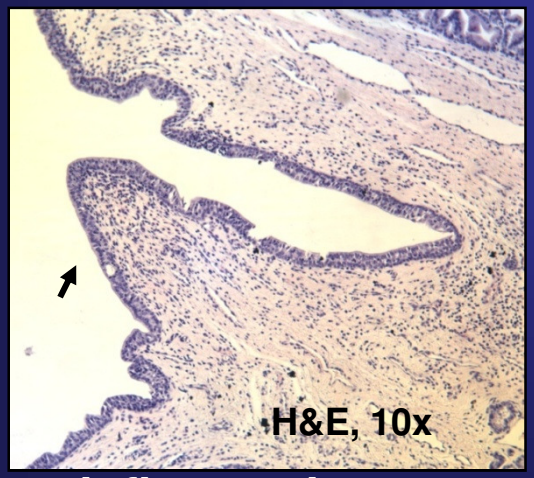
# Peri-urethral zone of the prostate at 12 wks

**Fibrosis**

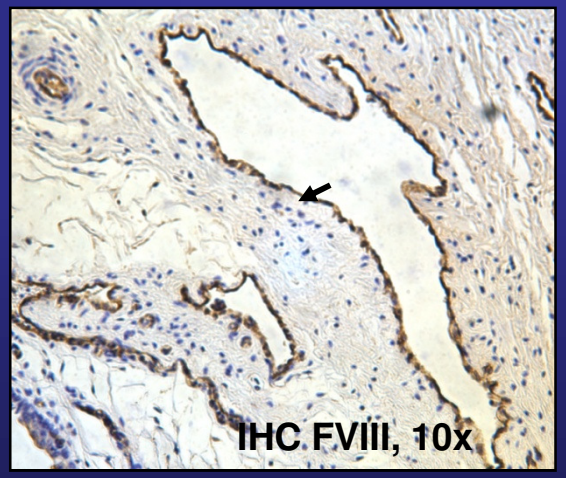



**Hemosiderosis**




**inflammation**

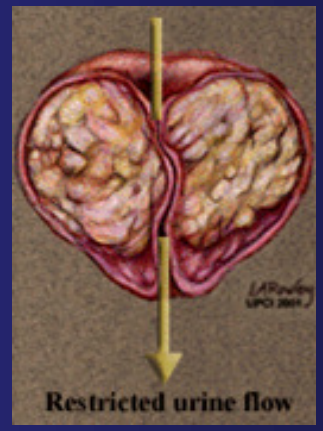


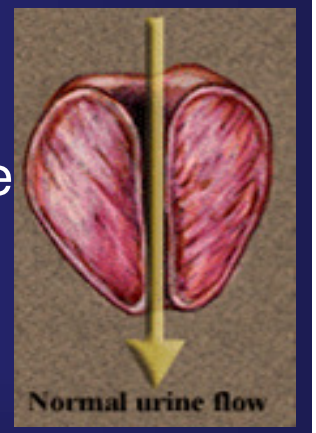

Fibrosis and hemosiderosis reflect necrosis

Urethelium and endothelium renewed

# Proof of Concept : VTP (PDT) for BPH

| | | |
|---|---|---|
| 1 wk | Damages to blood vessels (endothelium)<br>Blood cells in tissue (hemorrhages)<br>Necrosis in peri-urethral area and partial damage of urethelium<br>Acute inflammation | |
| 6-9wks | Urethelium & endothelium restored | Increase in prostatic urethral width or diameter |
| 12 wks | Oedema evident & fibrosis developing<br>Chronic inflammation | Decrease in maximal urethral and closure pressure<br>Lumen wider |
| 1 year | Fibrosis and inflammation | Improved parameters persisted |



# BPH: Conclusion and future directions

- Minimally invasive endoscopic laser procedure of short duration activating infused WST11 in blood vessels of the prostate rapidly translates into long lasting effects on urethra, including on parameters used to assess LUTS in BPH patients

- Could be easy to optimize for patients with mild- moderate LUTS

- « **Precaution and issue to address** »
  - Laser light may reach the bladder neck and cause damages
  - Tested insertion of fiber in a urinary catheter closed at the extremity near bladder but lost efficacy even if increase power of laser and fluence
  - NB: Not seen in phantom model
  - ? ballon inserted in the bladder with guide, pulled back to close the bladder neck and inflated prior positioning the fiber

- Selection of diffuser length in fibers vs. portion of urethra to treat

# PDT for PCa

# PCa: incidence, symptoms and screening

- Most common male malignancy in US
  - incidence of 1 man on 7 in lifetime (15.3%)
  - 230, 000 estimated new cases in 2014

- PCa can be lethal, 2nd cause of death by cancer in US
  - estimated 29,480 Americans will die from PCa in 2014

- No symptom unless advanced; incidently found in men seen for BPH

- Strongly influenced by aging
  - 40-50% pre-malignant lesions in 4th and 5th decade
  - 40-50% of men in their 8th decade have PCa

- Prevention is desirable but causes are unknown
  - risk factors, beside age: family history, ethnicity, lifestyle habits and diet

- Screening: not recommended any more
  - if done by age of ≥50 and younger if prevalent in family

# PCa therapies and opportunity for PDT

- Tx *vs.* risk categories (blood PSA & pathological biopsy data)
  - active surveillance (low risks), surgery (prostatectomy) and radiations if intermediate and high risks
  - risk categories are not always accurate (sampling issue at biopsy and pathological assessment)

  - **Debate**: overtreatment of clinically insignificant cancers *vs.* morbidity of therapy (impotence and incontinence
  - Need to identify more aggressive to only treat them
    - still, 25-30% recurrence after surgery and radiations
    - **Recurrence after radiation Tx was an opportunity for PDT**

- Statistics may change in years to come
  - May find cancer at more advanced stages

- More room to develop «**minimally invasive PDT**» for low risk Pca
  - some patients do not wish to be on active surveillance
  - repeated tests, waiting for results to be treated often increase anxiety
  - 25-30% progress in 2-3 years and require Tx

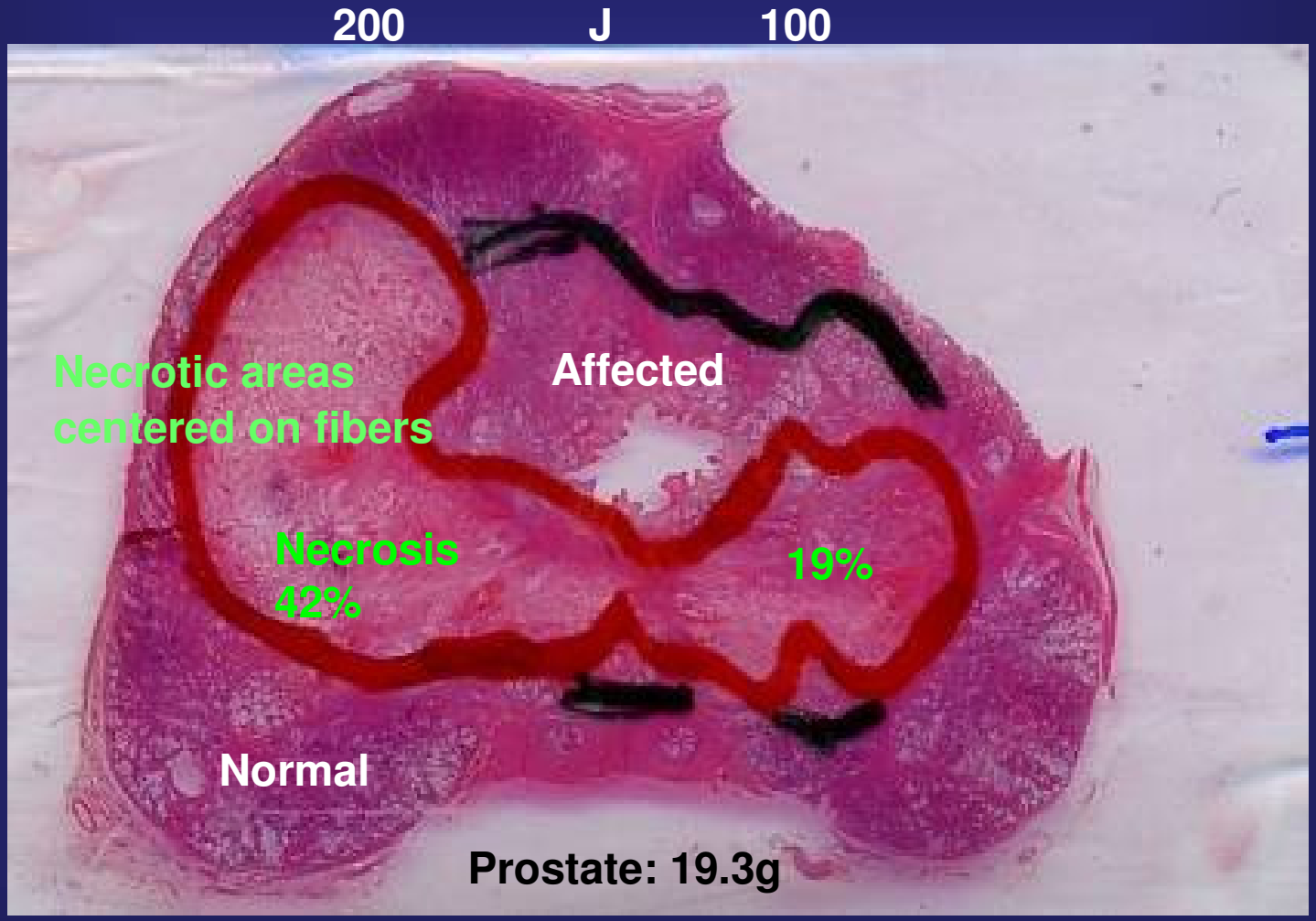
# WST09-Tookad for PDT in PCa

- WST09,1st generation of bacteriochlorophyll for clinical applications
  Trachtenberg et al. BJU Int, 2008
  Vascular-targeted photodynamic therapy (padoporfin, WST09) for recurrent prostate cancer after failure of external beam radiotherapy: a study of escalating light doses.
  - fibers in prostate parenchyma *via* a brachytherapy platform
  - trial stopped due to a few incidents attributed to WST09 poor solubility

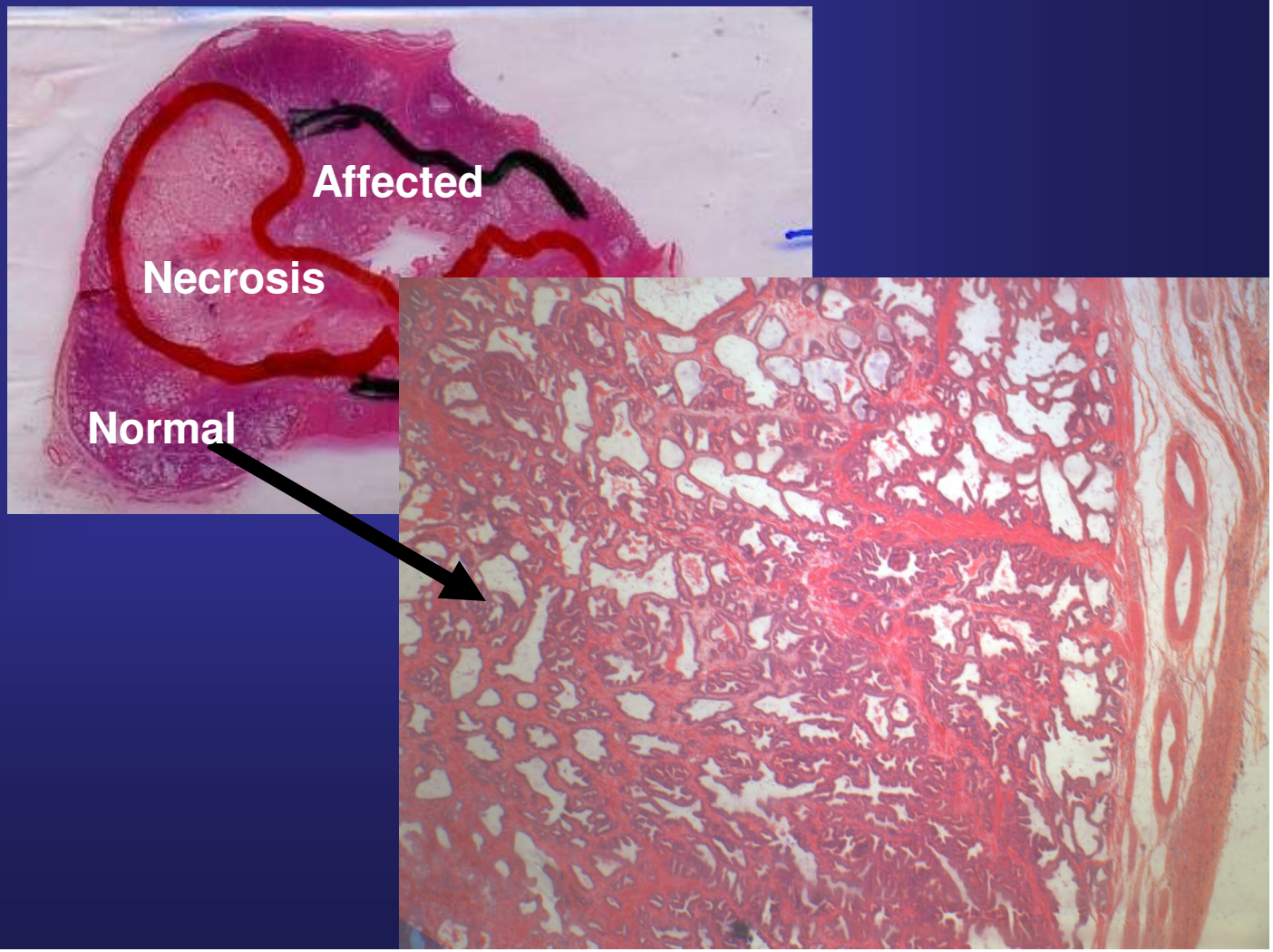
**Aim: Replace WST09 by WST11, new and highly soluble photosensitizer**

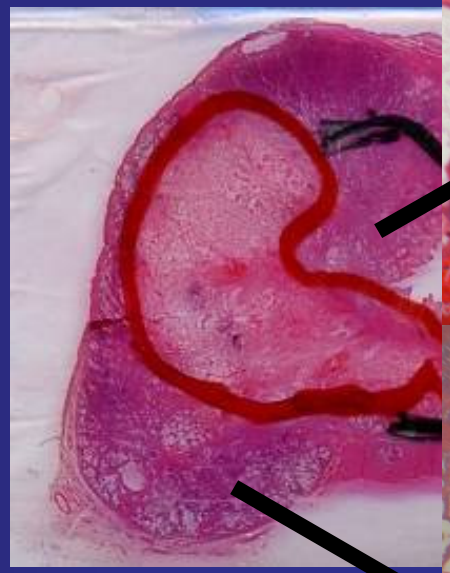
- Basis: pre-clinical studies with WST09 (A763nm) in dogs with prostate exposed by laparotomy to insert one fiber per lobe
  - light source150mW/cm A753nm
  - 100 vs. 200J with 1cm diffuser
  - Necrotic lesions assessed at 1wk – dose-escalation and optimization

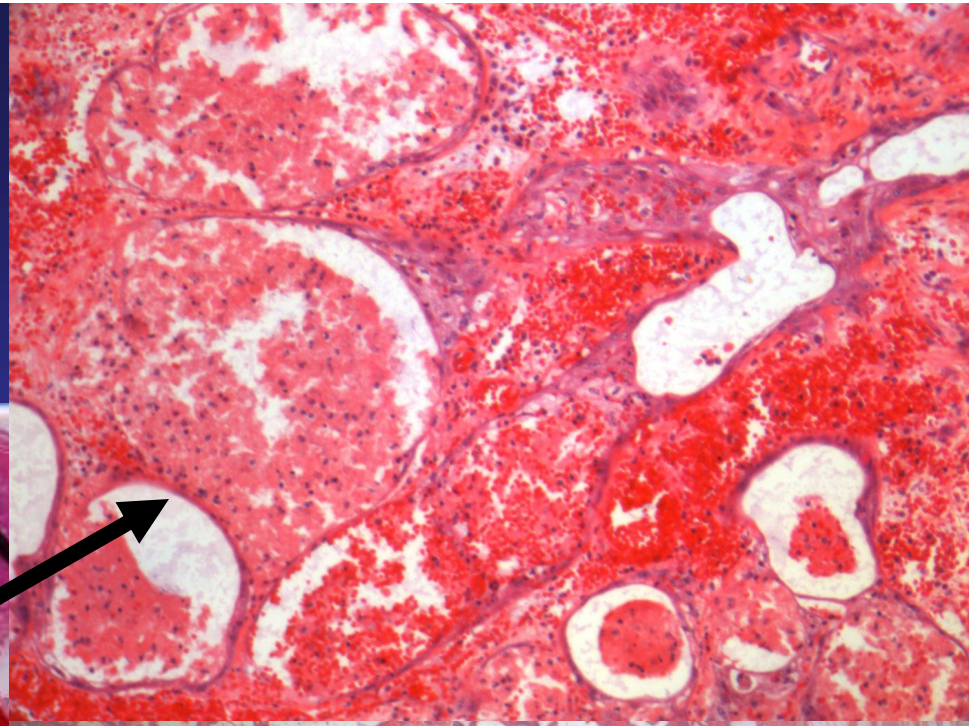
# Efficacy: Necrosis
## Microscopic analysis

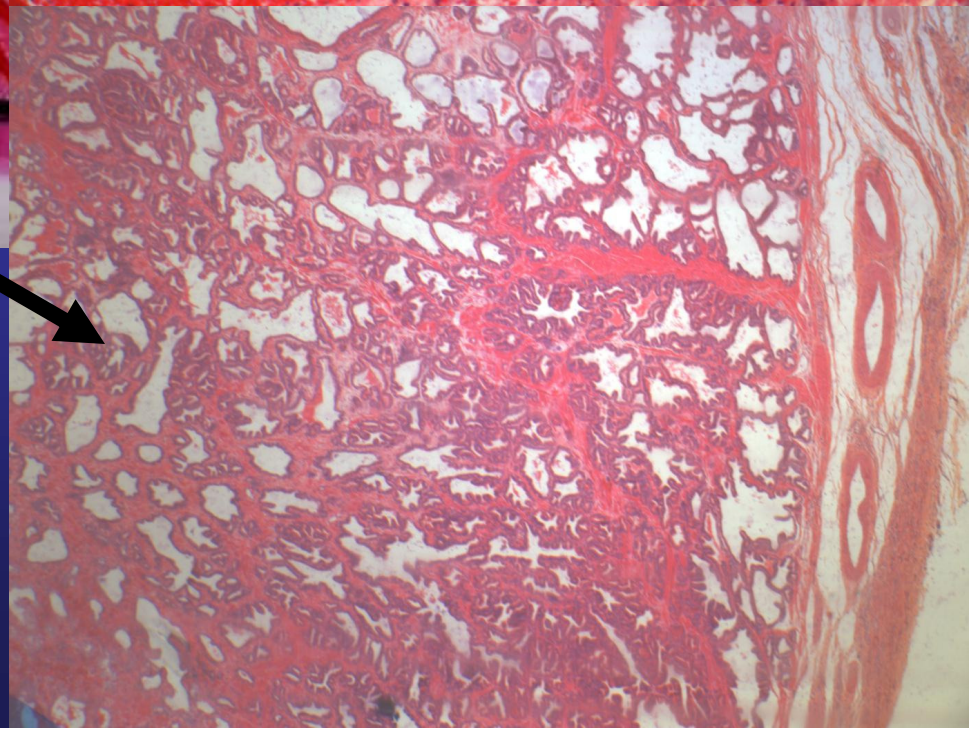


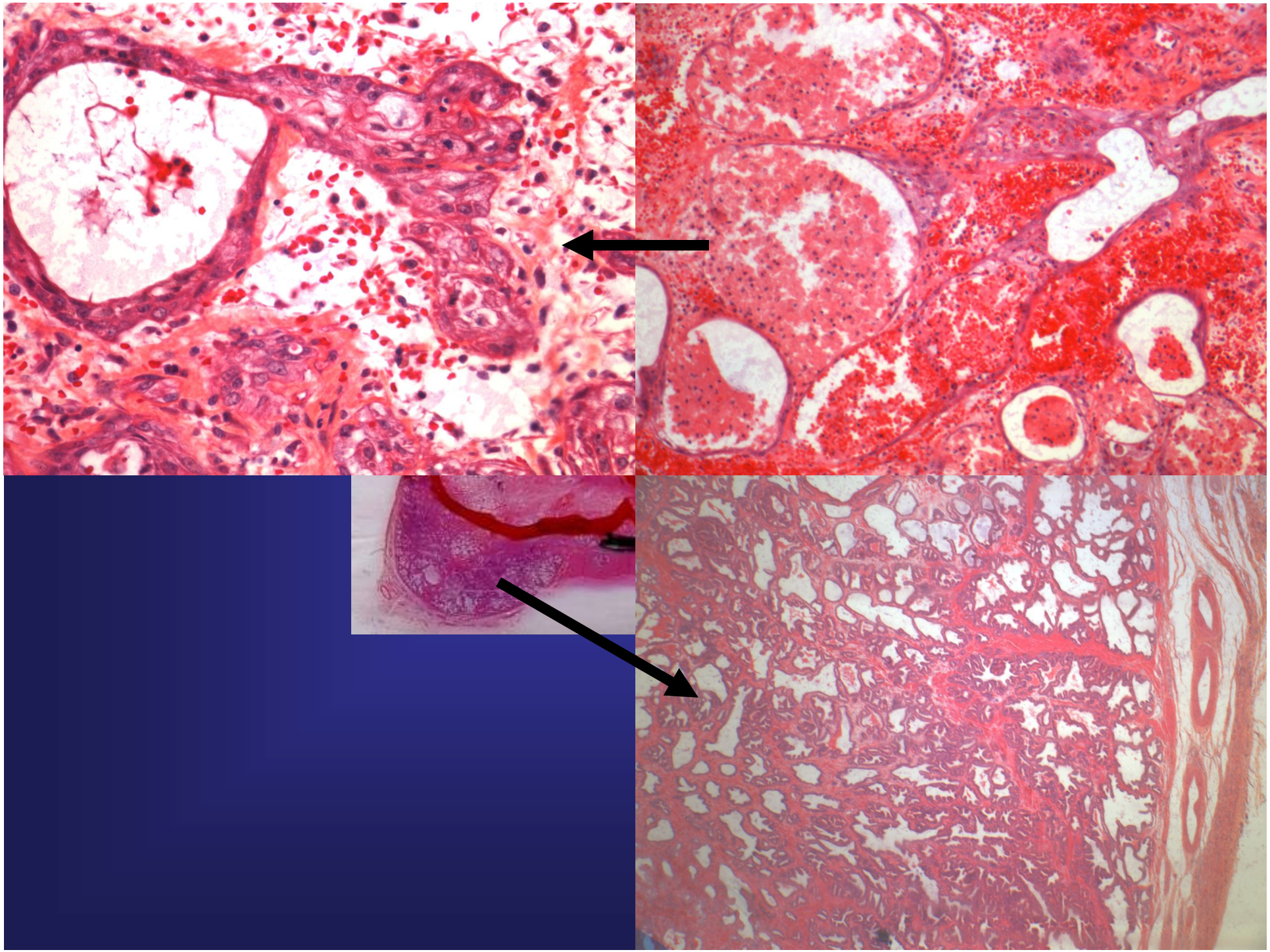
# Microscopy: histopathology

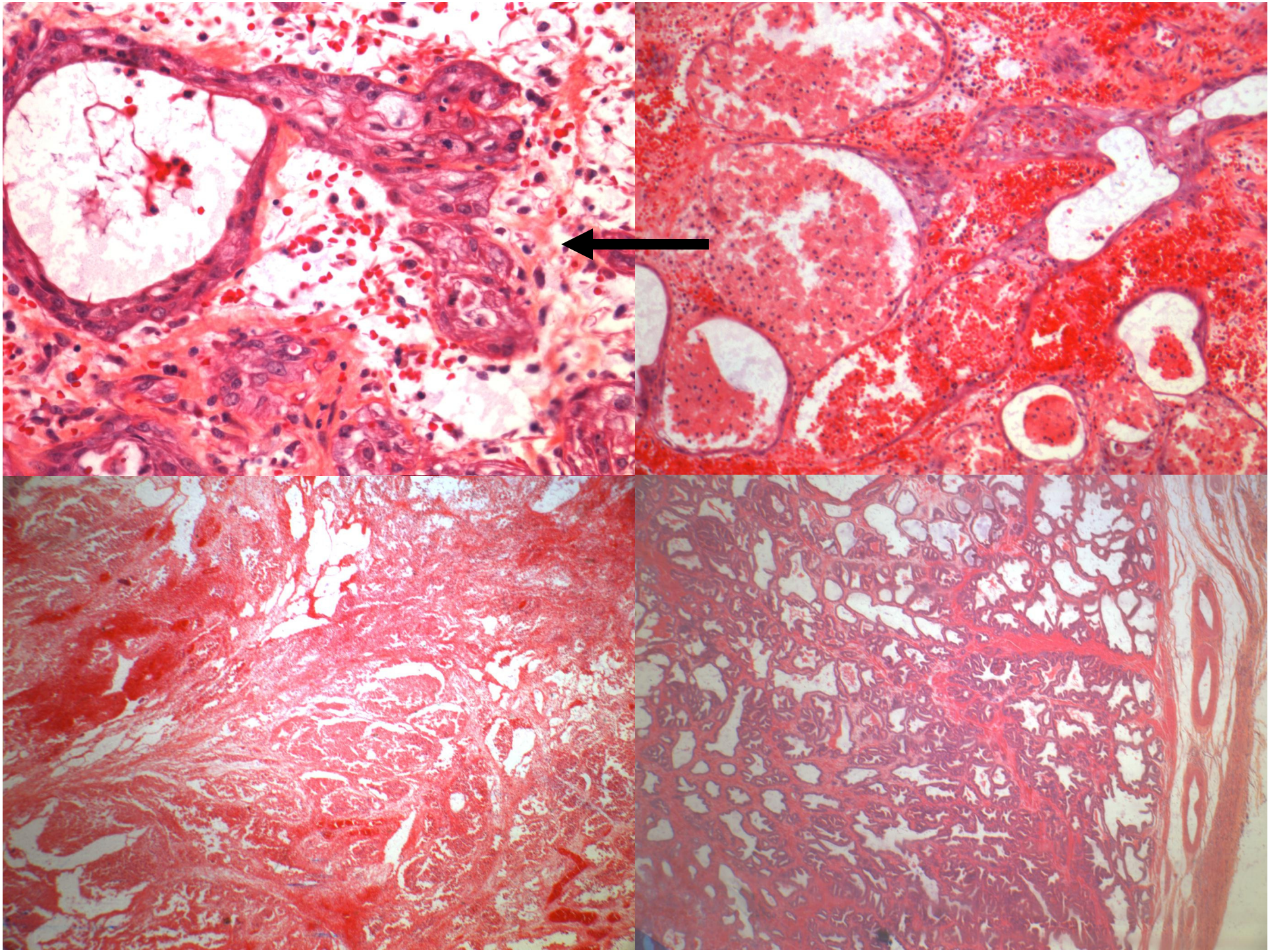






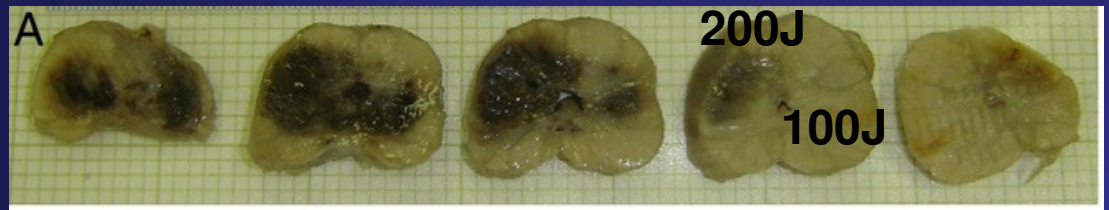


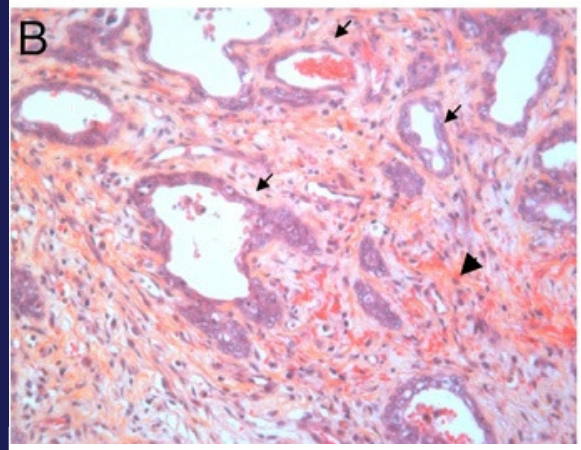


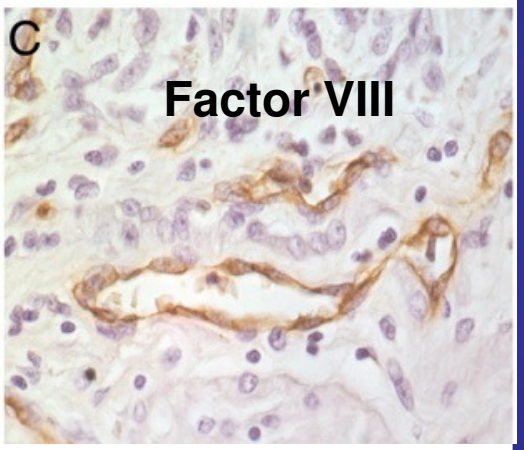


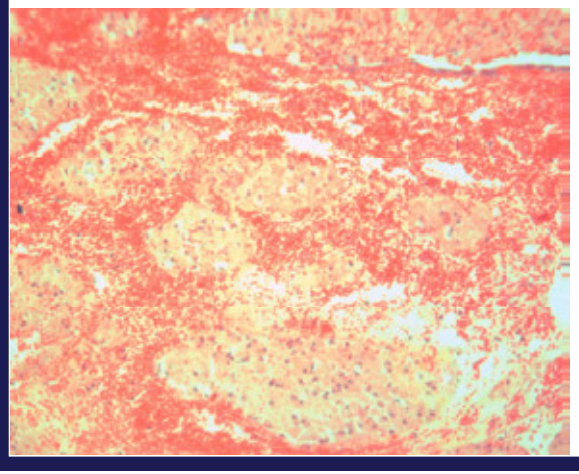
# PDT-induced visible hemorrhages and necrosis centered on treatment fiber in prostatic lobes

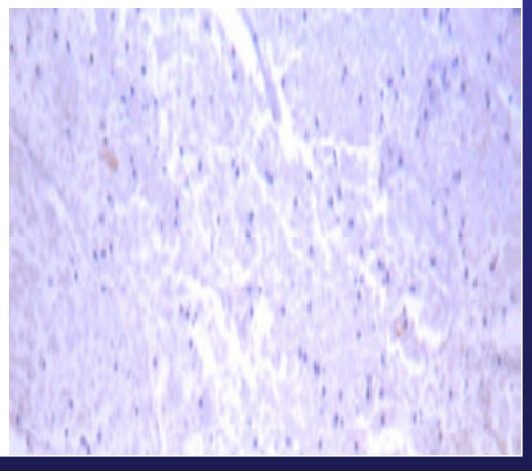
WST11-PDT 2 mg/kg; fluence 150 mW/cm; one fiber/lobe; 1 cm diffuser



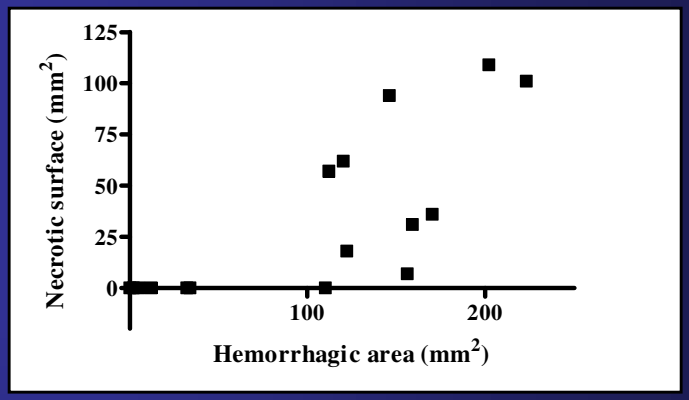





Hemorrhages at 200J more pronounced than at 100J
- hemorrhagic > necrotic areas




- histology: necrosis surrounding fiber with loss of glands and damaged blood vessels
- disorganized atrophic glands. inflammation, intact vessels in periphery (non-necrotic zone)

# Efficacy: dose escalation and necrosis

**Table 2. Dose-escalation of WST11: VIP induced hemorrhages and necrosis in the dog prostate**

| Dog | Prostate | | Infusion | *Energy | Hemorrhages | | | Necrosis (N) | |
|---|---|---|---|---|---|---|---|---|---|
| # | Weight (g) | Urethral length (cm) | WST11 (mg/kg) | (J/cm) lobe 1/lobe 2 | Prostate slices (+/n) lobe 1/lobe 2 | Spreading cranial-caudal axis (cm) | Intensity (0-6+) lobe 1/lobe 2 | Surface ($S_N$) ($mm^2$) lobe 1/lobe 2 | Relative surface (%) lobe 1/lobe 2 |
| 1 | 13.1 | 3.0 | 2 | 100/200 | (3/5)/(4/5) | 1.8/2.4 | 3+/3+ | 0/0 | 0/0 |
| 2 | 12.6 | 2.5 | 2 | 100/200 | (4/5)/(4/5) | 2.0/2.0 | 3+/4+ | 0/0 | 0/0 |
| 3 | 49.0 | 4.4 | 2 | 100/200 | (2/7)/(2/7) | 1.3/1.3 | 1+/1+ | 0/0 | 0/0 |
| 4 | 9.6 | 3.0 | 2 | 100/200 | (4/7)/(4/7) | 1.7/1.7 | 3+/4+ | 7/9 | 6/6 |
| 5 | 18.7 | 4.0 | 4 | 100/200 | (3/7)/(4/7) | 1.7/2.3 | 1+/3+ | 0/57 | 0/29 |
| 6 | 19.3 | 3.0 | 4 | 100/200 | (3/5)/(4/5) | 1.8/2.4 | 2~3+/5+ | 25/101 | 23/41 |
| 7 | 24.3 | 3.7 | 7.5 | 100/200 | (3/7)/(4/7) | 1.6/2.1 | 4+/5+ | 0/31 | 0/10 |
| 8 | 23.5 | 3.4 | 7.5 | 100/200 | (4/6)/(4/6) | 2.3/2.3 | 3+/4+ | 57/62 | 16/15 |
| 9 | 20.4 | 3.8 | 10 | 100/200 | (4/7)/(5/7) | 2.2/2.7 | 4~5+/5+ | 14/36 | 10/19 |
| 10 | 10.2 | 2.5 | 10 | 0/0 | (0/6)/(0/6) | 0/0 | 0/0 | 0/0 | 0/0 |
| 11 | 20.0 | 3.4 | 15 | 100/200 | (4/7)/(4/7) | 1.9/1.9 | 1+/2+ | 0/0 | 0/0 |
| 12 | 18.8 | 3.5 | 15 | 100/200 | (3/7)/(3/7) | 1.5/1.5 | 1+/1+ | 0/0 | 0/0 |
| 13 | 21.9 | 3.5 | 20 | 100/200 | (3/5)/(5/5) | 2.1/3.5 | 2+/6+ | 12/94 | 4/25 |
| 14 | 18.3 | 3.7 | 20 | 100/200 | (3/6)/(4/6) | 1.9/2.5 | 2+/2+ | 0/0 | 0/0 |
| 15 | 19.9 | 3.7 | 30 | 100/200 | (2/6)/(3/6) | 1.2/1.9 | 0.5+/3+ | 0/18 | 0/11 |
| 16 | 18.2 | 3.0 | 30 | 100/200 | (5/5)/(5/5) | 3.0/3.0 | 2+/6+ | 17/109 | 13/39 |

Tx lobes:100% hemorrhages and 50% necrosis, best at ~4-7.5mg/kg WST11

# Efficacy: optimization through light parameters
## Focus on necrotic surface

**Table 3. Optimization of illumination to increase necrosis in the dog prostate**

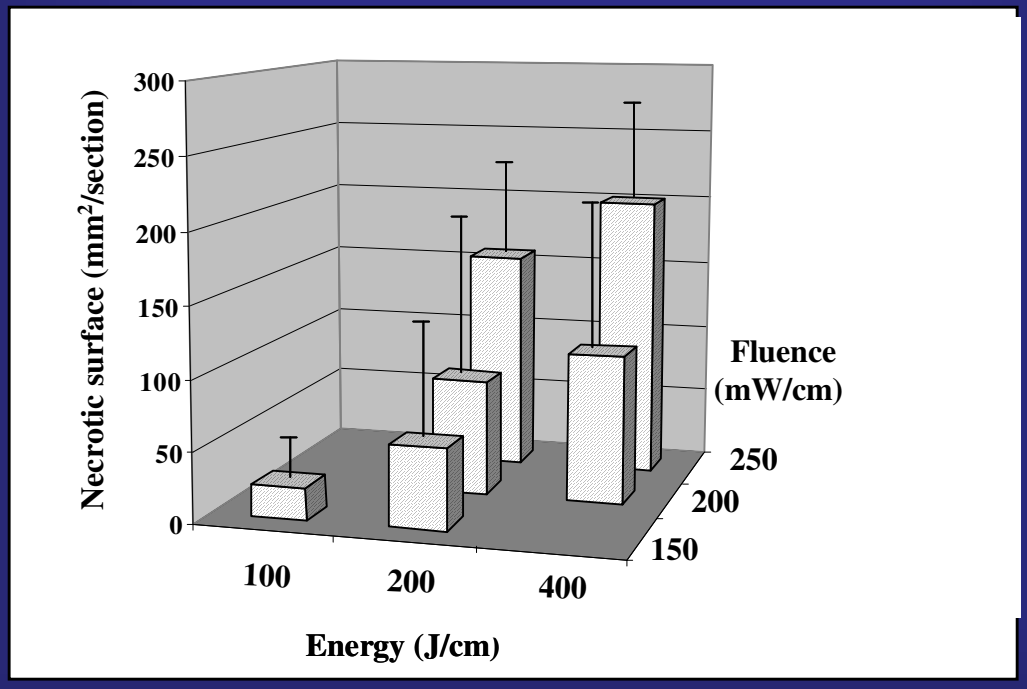
| Dog | Prostate | Infusion | Laser illumination | | Necrosis (N) | |
|---|---|---|---|---|---|---|
| # | Weight (g) | WST11 (mg/kg) | Fluence (mW/cm) | Energy (J) lobe 1/lobe 2 | Surface ($S_N$) ($mm^2$) lobe 1/lobe 2 | Relative surface (%) lobe 1/lobe 2 |
| 17 | 21.3 | 5 | 200 | 200/400 | 69/73 | 31/27 |
| 18 | 33.1 | 5 | 200 | 200/400 | 221/226 | 72/80 |
| 19 | 7.5 | 5 | 200 | 200/400 | 0/14 | 0/9 |
| 20 | 9.9 | 5 | 200 | 200/400 | 36/109 | 26/57 |
| 21 | 15.2 | 2 | 200 | 200/400 | 0/0 | 0/0 |
| 22 | 28.1 | 2 | 200 | (200/400)*2 | 0/0 | 0/0 |
| 23 | 21.6 | 5 | 250 | (200/200)*2 | 0/0 | 0/0 |
| 24 | 22.1 | 5 | 250 | 200*2/400 | 185/207 | 58/60 |
| 25 | 22.8 | 5 | 250 | (200/400)*2 | 158/252 | 48/75 |
| 26 | 39.1 | 5 | 250 | 400/400*2 | 196/239 | 54/67 |
| 27 | 17.0 | 5 | 250 | (200/400)*2 | 152/192 | 49/59 |
| 28 | 17.0 | 5 | 250 | (200/400)*2 | 195/212 | 59/66 |
| 29 | 14.8 | 5 | 250 | (200/400)*2 | 227/250 | 77/78 |
| 30 | 12.7 | 5 | 250 | (200/400)*2 | 124/138 | 47/53 |
| 31 | 21.2 | 5 | 250 | (200/400)*2 | 188/275 | 50/67 |
| 32 | 8.5 | 5 | 250 | (200/400)*2 | 25/48 | 13/25 |
| 33 | 17.0 | 2 | 250 | 200/200*2 | 140/161 | 46/55 |
| 34 | 19.0 | 2 | 250 | 400/400*2 | 247/231 | 73/73 |
| 35 | 20.2 | WST09 2 | 150 | 200/200 | 105/146 | 36/48 |
| 36 | 15.9 | WST09 2 | 150 | 200/200*2 | 176/238 | 60/77 |
| 37 | 18 | WST09 2 | 150 | 200/200*2 | 76/202 | 30/77 |

Significant tissue destruction achieved

Comparable to WST09

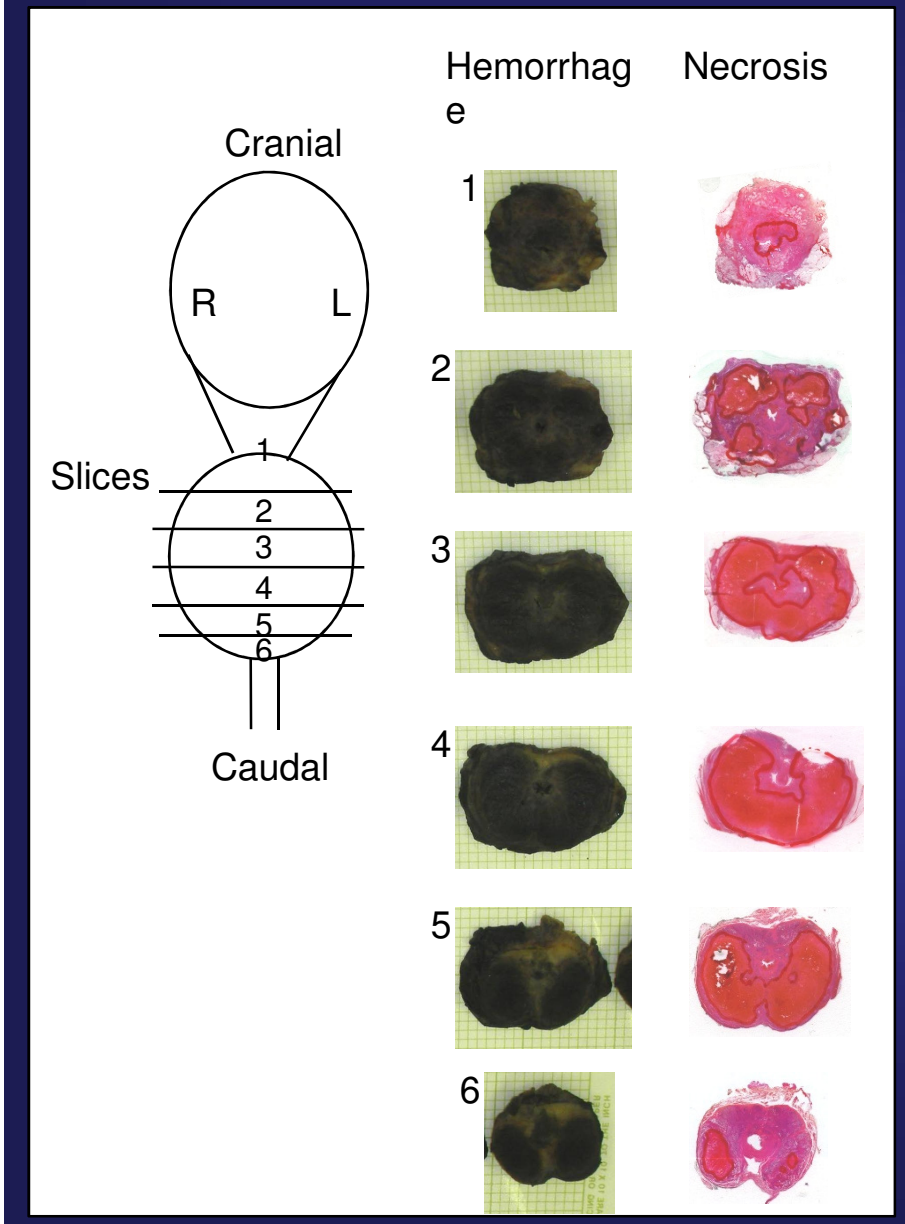
# Influence of laser light fluence and energy delivered within each lobe on necrotic areas induced by activated WST11

*sections from most hemorrhagic prostate slices

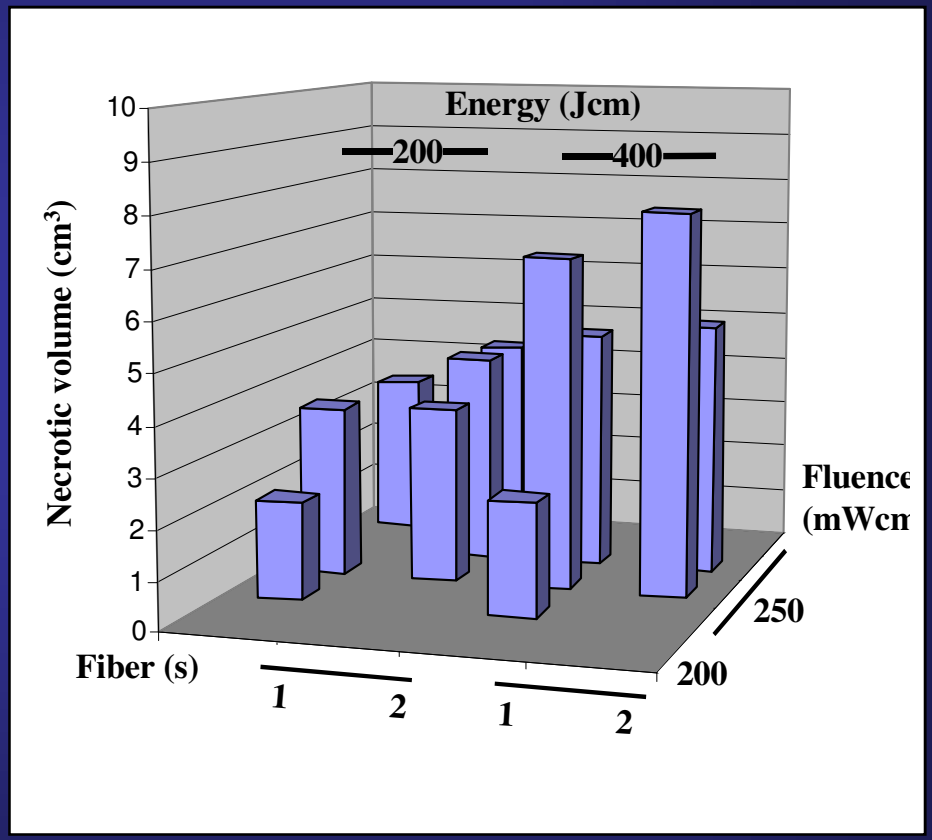



Power and energy delivered are determinant for PDT efficacy with WST11

# From necrotic area to volume of ablated tissue




necrotic area/section/lobe reported in volume based on slice thickness




Number of fibers is critical to maximize tissue ablation

# Conclusion

- Pre-clinical PDT studies with WST11 (called TOOKAD® soluble) have refined the definition of necrotic lesions: visible hemorrhages are not sufficient
- Provided insights on optimal laser light parameters and doses to maximize necrosis in the prostate
- Procedure is safe and rapid
- Efficient, with necrosis comparing favorably to WST09
- Mechanism: primarily vascular
- PDT results in large volume of ablated prostate tissue

VTP-WST11 is an attractive minimally invasive

therapy for localized prostate cancer

(Chevalier et al., J Urol 186; 30209, 2011)

- Set the stage for clinical trial in patients with localized PCa under Dr Emberton, UK; BJU Int. Oct 2013 and May 2014

# Team Members

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* Thank you - Merci *

# Efficacy: ablated prostate tissue

**Table 4. Volume of ablated prostate tissues**

| Dog # | Product (mg/kg) | Fluence (mW/cm) | Energy (J/cm) lobe 1/lobe 2 | Volume necrosis ($V_N$) ($cm^3$) lobe 1/lobe 2 | Total volume necrosis ($V_{NT}$) ($cm^3$) |
|---|---|---|---|---|---|
| 17 | WST11 5 | 200 | 200/400 | 1.5/1.0 | 2.5 |
| 18 | WST11 5 | 200 | 200/400 | 5.3/6.1 | 11.4 |
| 19 | WST11 5 | 200 | 200/400 | 0/0.2 | 0.2 |
| 20 | WST11 5 | 200 | 200/400 | 1.2/1.8 | 3.0 |
| 24 | WST11 5 | 250 | 200*2/400 | 4.0/6.8 | 10.8 |
| 25 | WST11 5 | 250 | (200/400)*2 | 2.3/6.7 | 9.0 |
| 26 | WST11 5 | 250 | 400/400*2 | 3.0/5.6 | 8.6 |
| 27 | WST11 5 | 250 | (200/400)*2 | 5.3/4.8 | 10.1 |
| 28 | WST11 5 | 250 | (200/400)*2 | 6.2/6.6 | 12.8 |
| 29 | WST11 5 | 250 | (200/400)*2 | 7.0/7.2 | 14.2 |
| 30 | WST11 5 | 250 | (200/400)*2 | 3.2/2.7 | 5.9 |
| 31 | WST11 5 | 250 | (200/400)*2 | 5.0/7.2 | 12.2 |
| 32 | WST11 5 | 250 | (200/400)*2 | 1.2/0.6 | 1.8 |
| 33 | WST11 2 | 250 | 200/200*2 | 3.5/3.6 | 7.1 |
| 34 | WST11 2 | 250 | 400/400*2 | 6.8/7.8 | 14.6 |
| 36 | WST09 2 | 150 | 200/200*2 | 3.3/3.1 | 6.4 |
| 37 | WST09 2 | 150 | 200/200*2 | 5.1/3.5 | 8.6 |

Necrotic volume represents ~50%) of the whole prostate (~10cm3) based on mean prostate weight of 19.5g

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