UniversitätsKlinikum Heidelberg

Heidelberg First Clinical Experience with Profound Medical Inc.'s MRI-Guided TULSA-PRO

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MRI-GUIDED TULSA-PRO

Novel minimal-invasive treatment of localised prostate cancer

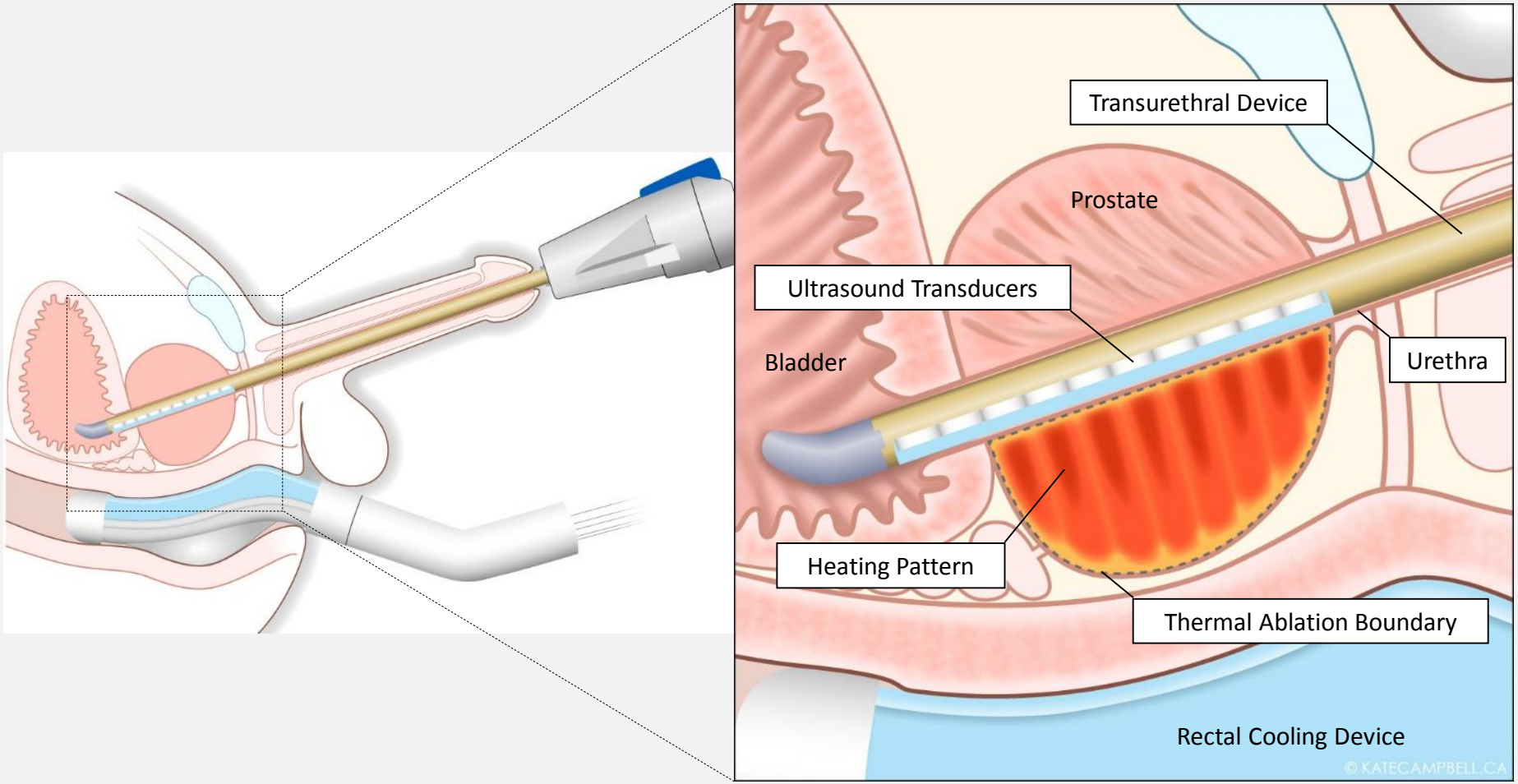
Main objectives:

Improve ultrasound prostate ablation (e.g. HIFU) by

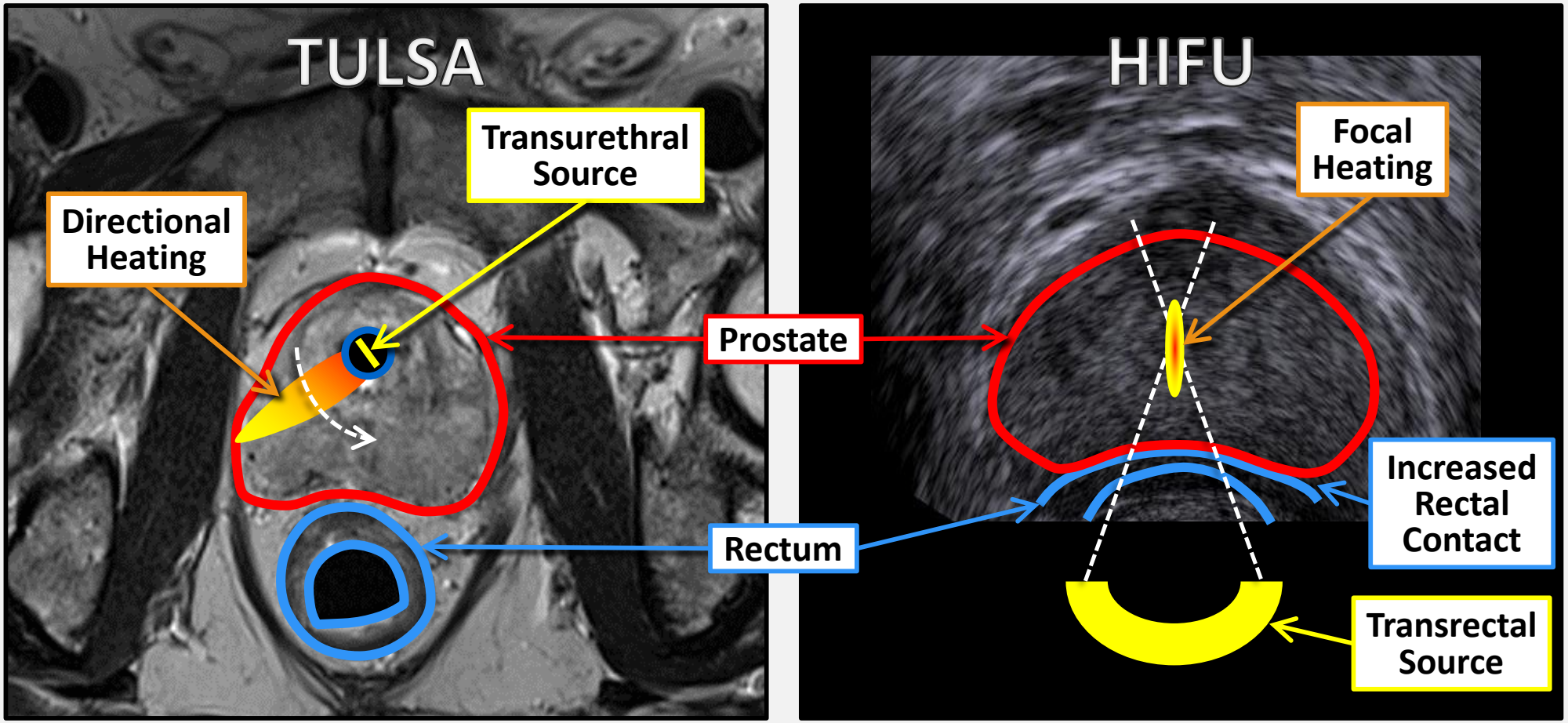
- Better treatment control
- MRI Thermometry = Dose
- Dose control = Focal
- Better safety profile (fewer side effects)

Ultimately: *better* cancer control with
better safety and preservation of quality of life

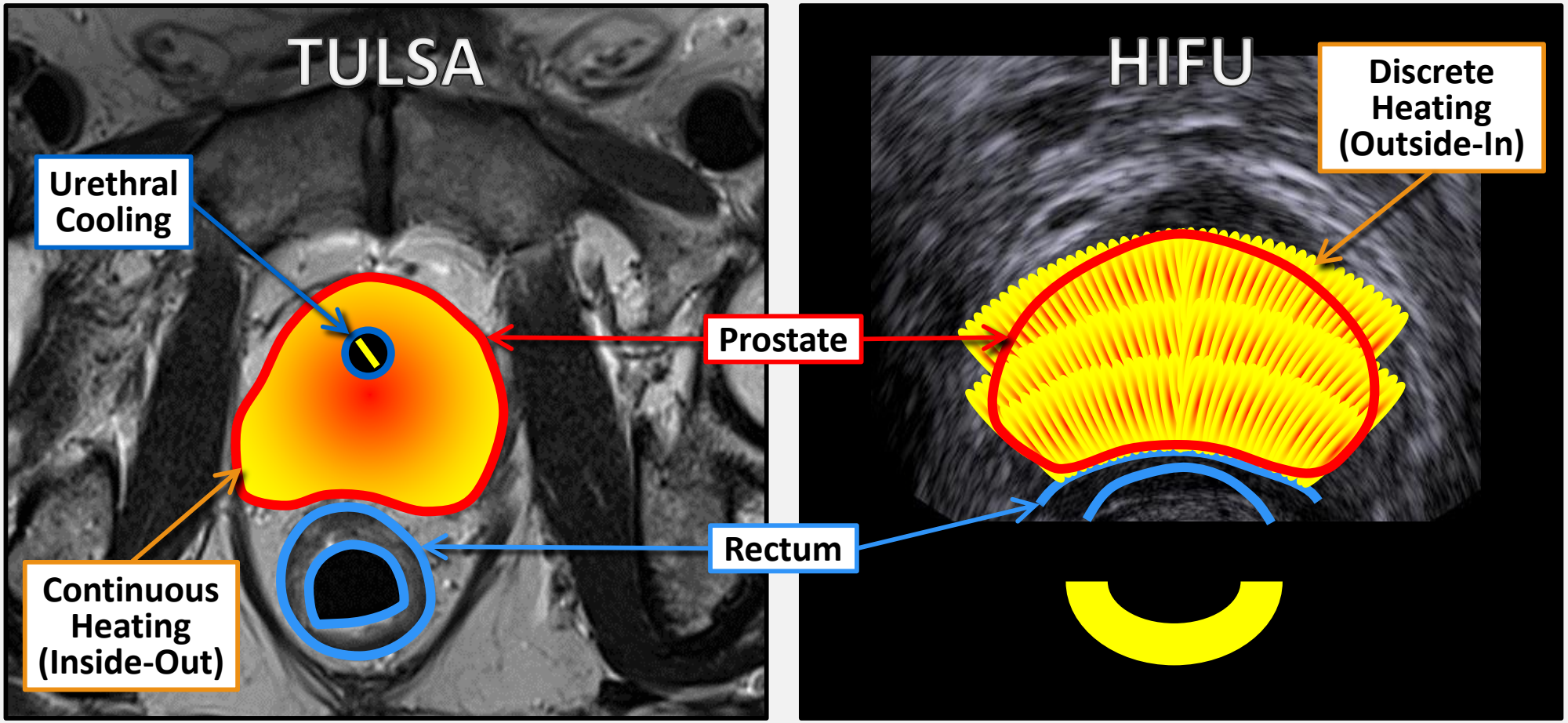
TULSA-PRO DEVICE



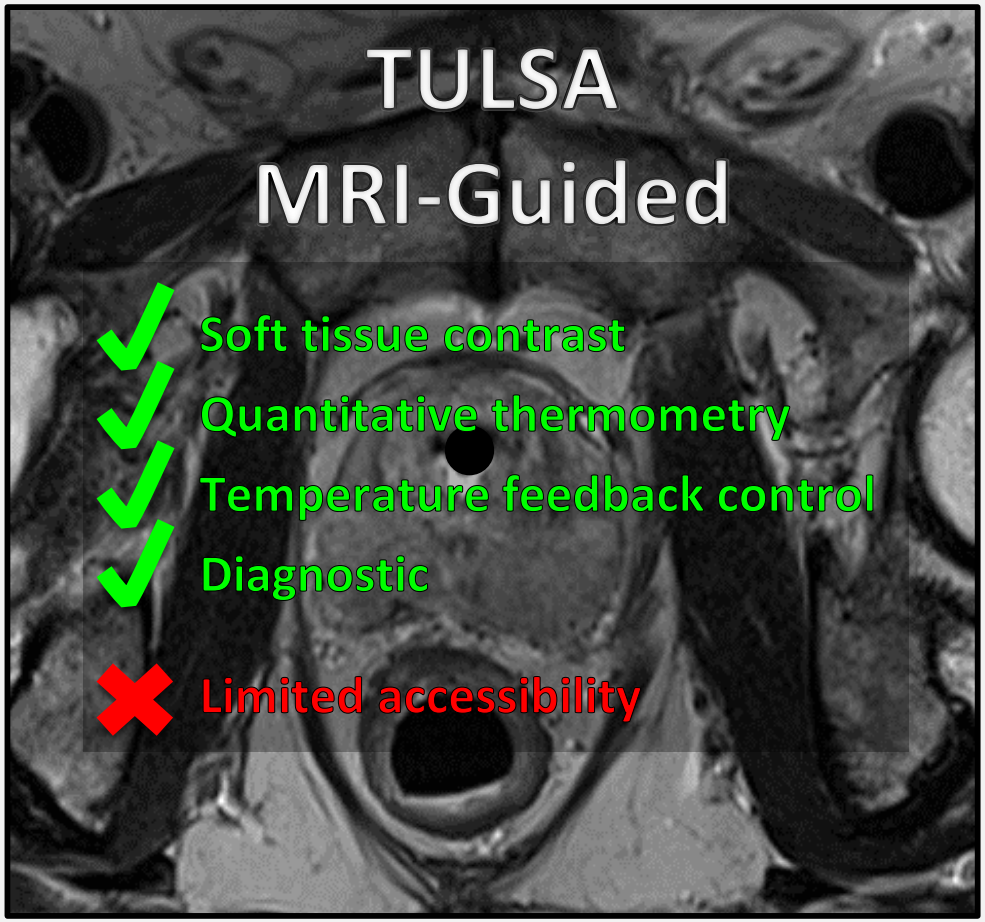
TULSA-PRO DIFFERENCE: ANATOMY

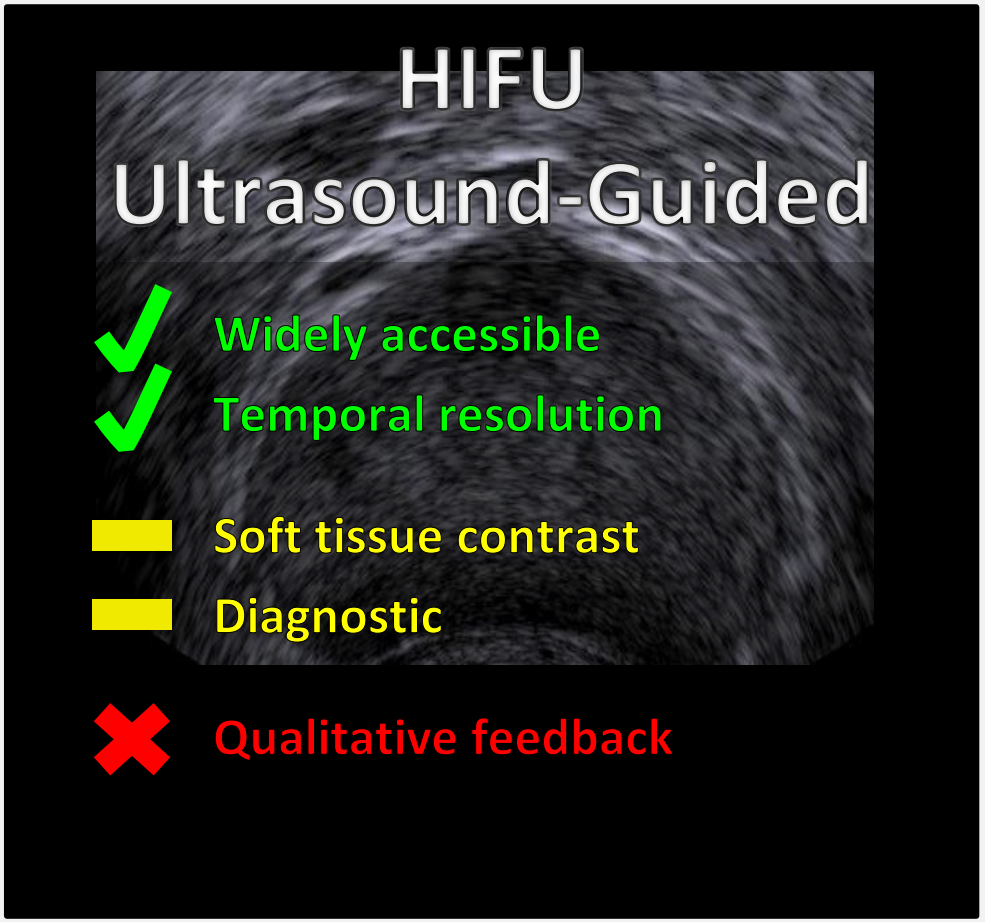


TULSA-PRO DIFFERENCE: TREATMENT

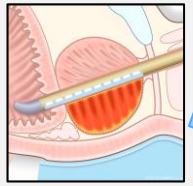


TULSA-PRO DIFFERENCE: IMAGING





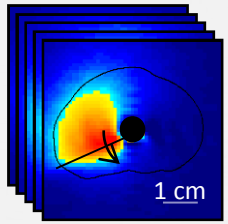
MRI-GUIDANCE



1 MRI Thermometry Acquisition

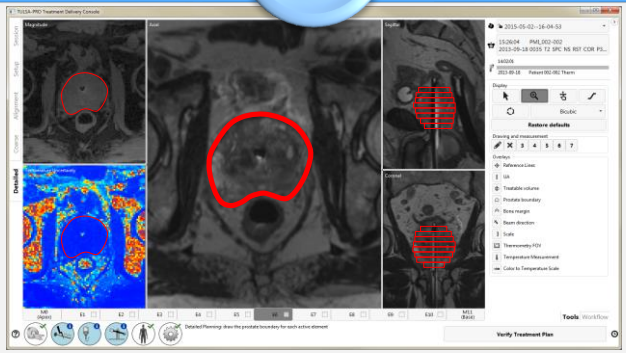
2 Temperature Feedback Control

3 Adjust Power, Frequency, Rotation Rate



Device Positioning

Planning

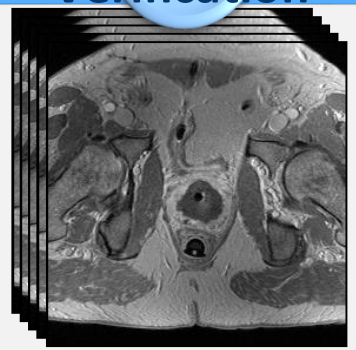


Precise Treatment Planning

Treatment

40 min

CE-MRI Verification



Visualization of NPV

PHASE I STUDY DESIGN

Study Design

- Prospective, multi-center, single-arm

Inclusion Criteria

- Age ≥ 65 years
- Low-/intermediate-risk prostate cancer
  - Biopsy confirmed organ-confined prostate cancer: cT1c or T2a, N0, M0
  - PSA ≤ 10 ng/ml
  - Gleason score 3+3 (Germany/USA), ≤ 3+4 (Canada)
- No prior prostate cancer treatment

Endpoints

- **Primary:** Safety (adverse events) and Feasibility (precise heating), 1-year follow-up
- **Exploratory:** Efficacy (PSA and Biopsy) and QoL (patient questionnaire), 5-year follow-up

PATIENT RECRUITMENT

Recruitment: Entire Study

- 30 patients enrolled: March 2013 – March 2014
- Clinical trial sites in 3 jurisdictions, all under same protocol
  - Urology / DKFZ (Heidelberg, Germany): 14 patients
  - Western University (London ON, Canada): 12 patients
  - William Beaumont Hospital (Royal Oak MI, United States): 4 patients

Screening: Heidelberg – 82 Patients

- N = 47 Active Surveillance (57.3%)
- N = 14 TULSA-PRO (17.1%)
- N = 11 Radical DaVinci Px (13.4%)
- N = 6 Radiotherapy (7.3%)
- N = 4 “Wait and see” (4.9%)

PATIENT PREPARATION

- **General Anesthesia**
- **GI anti-spasmodic drug**
  - Eliminate peristaltic motion of the colon which can cause artifacts on MRI thermometry
- **Supra-Pubic Catheter (SPC)**
  - Drains bladder prior and during treatment
  - Eliminate filling of bladder after treatment planning and during treatment
  - Removal at 2-week follow-up visit after treatment
- **Guidewire**
  - Aid insertion of transurethral device

TULSA-PRO DEVICES

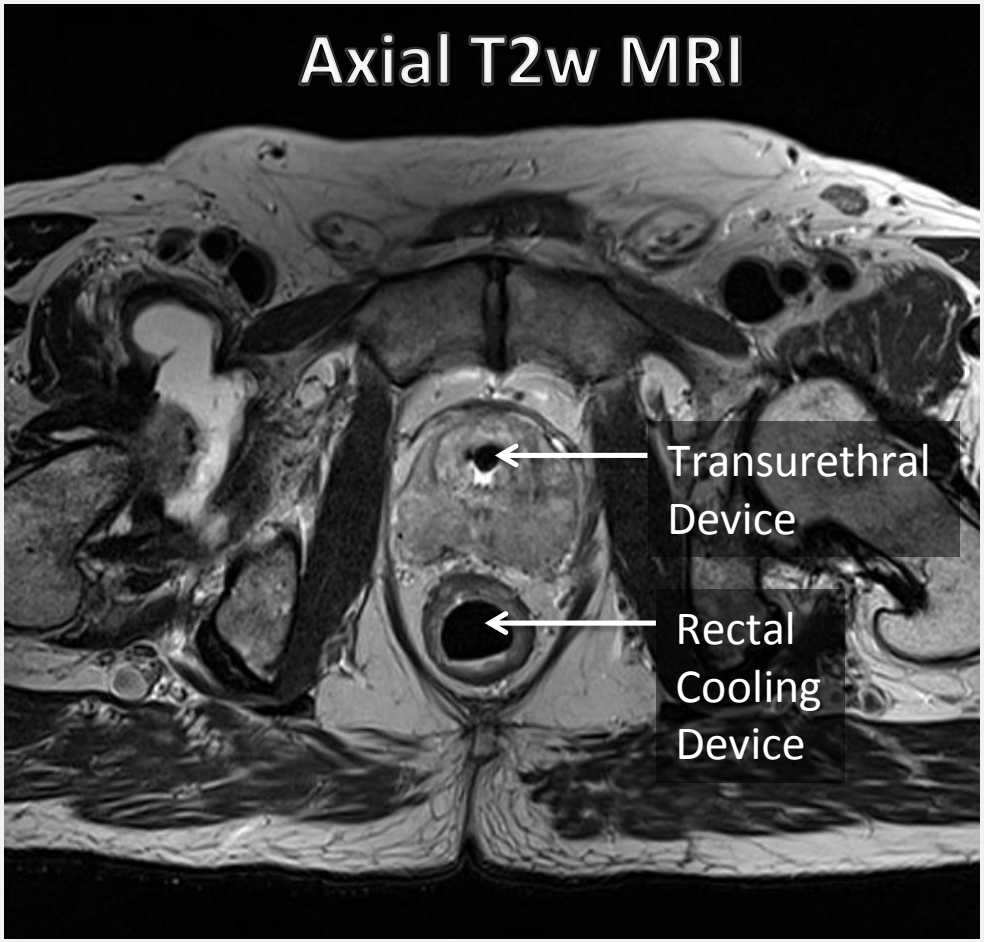
Urethral Device

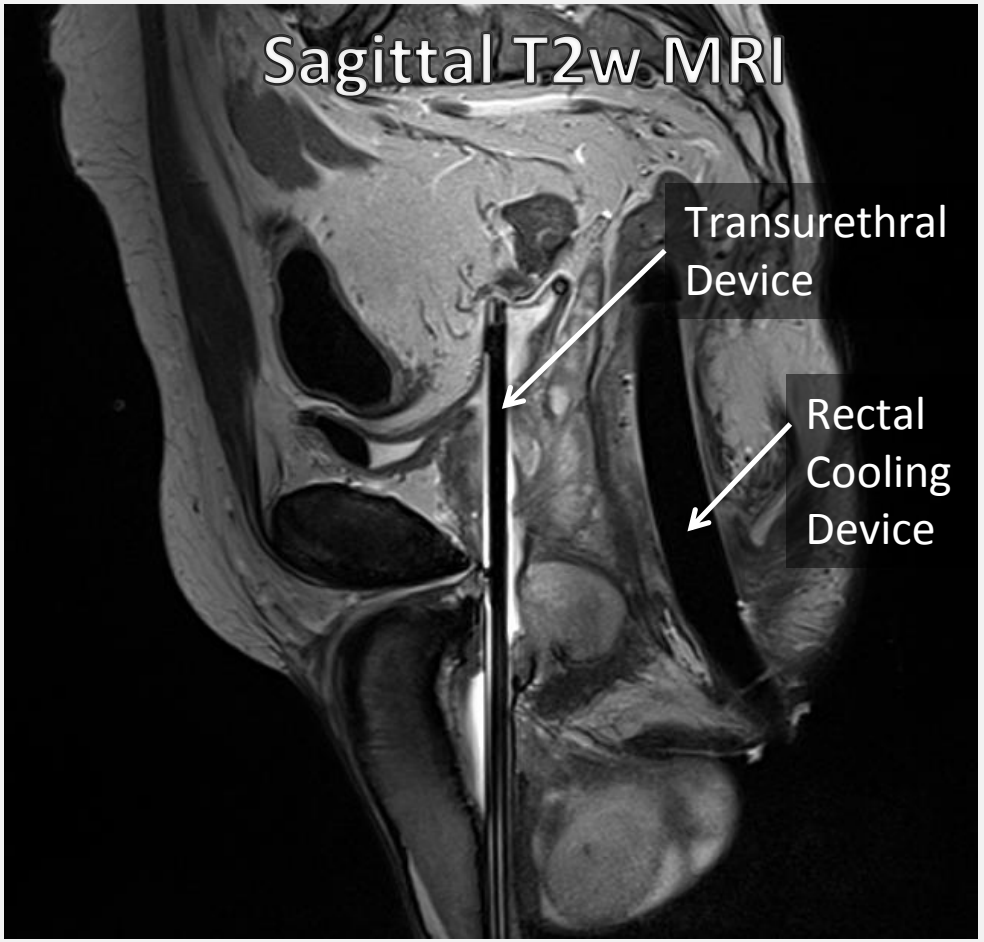
10 independent ultrasound transducer elements; 4 & 13 MHz; 0 to 4 W acoustic / element
Rigid catheter; Size 22 French; Sterile, single-use, disposable

Rectal Cooling Device

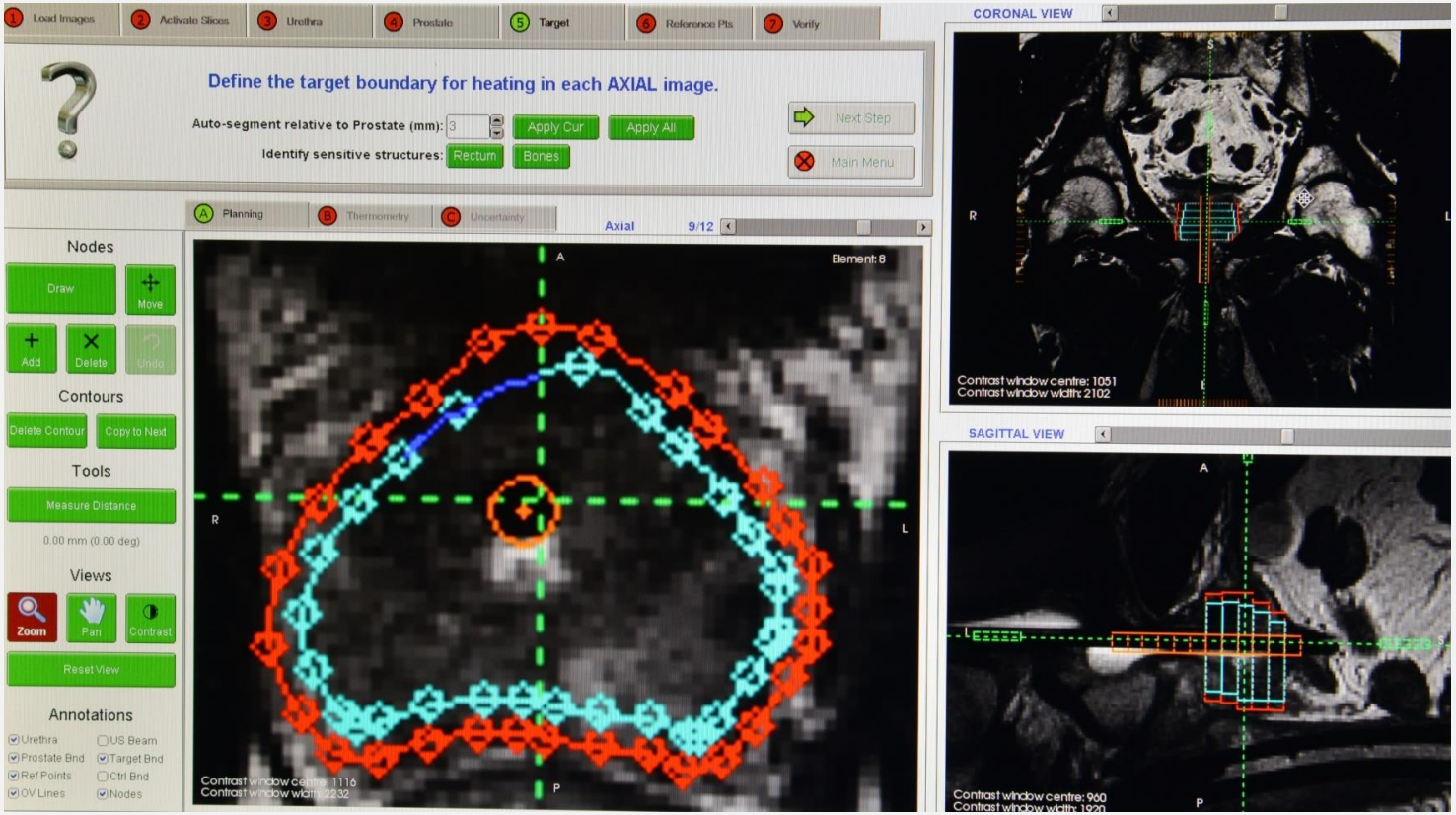
Passive cooling; Non-sterile, single-use, disposable

MRI-GUIDED DEVICE POSITIONING



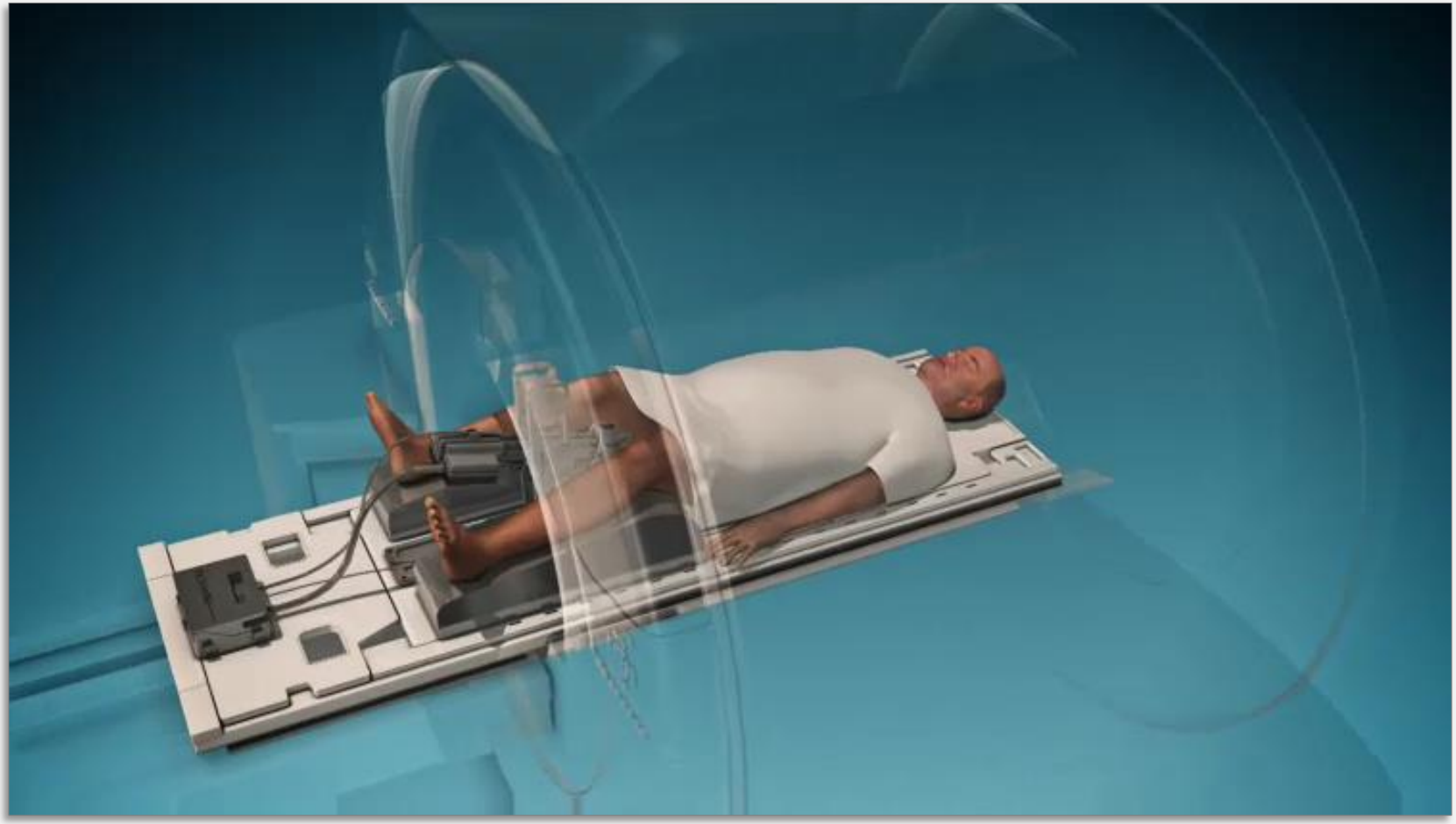


PHASE I TREATMENT PLANNING



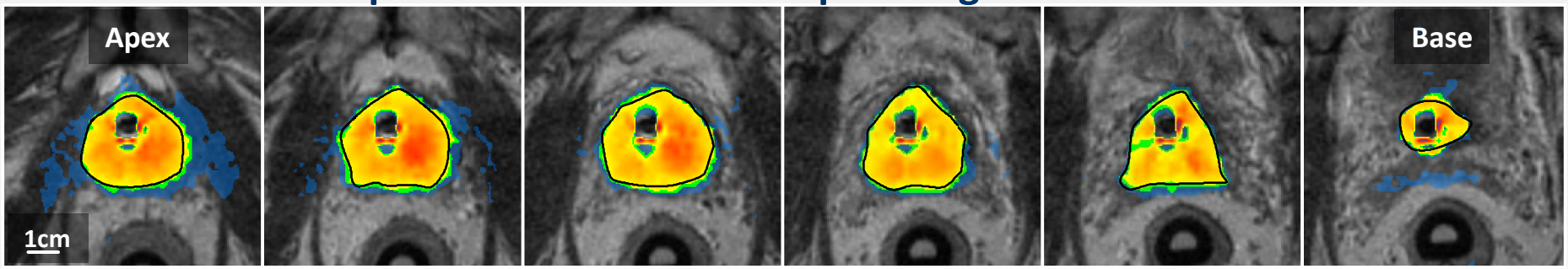
- Conservative whole-gland treatment planning
- 3 mm safety margins at capsule and apex
- 10% residual viable tissue expected at periphery

MRI-GUIDED TREATMENT

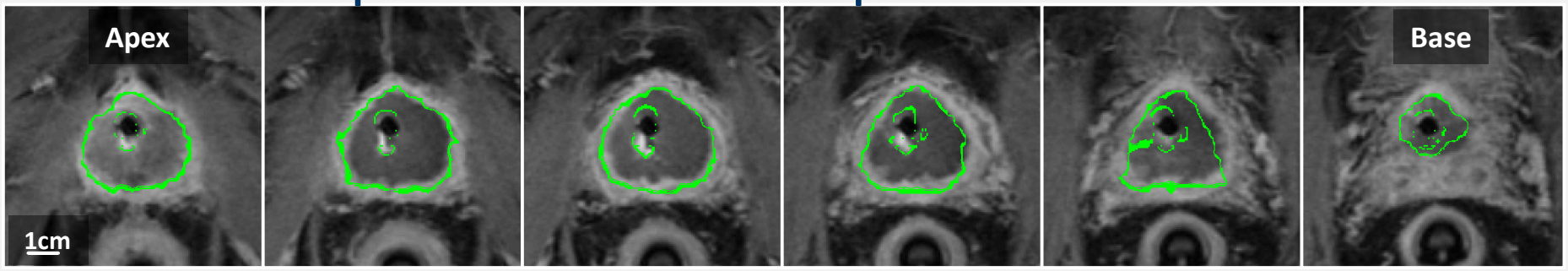


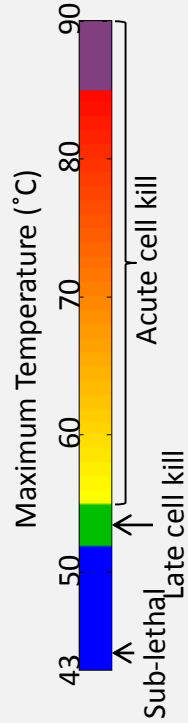
TREATMENT ASSESSMENT

Maximum Temperature > 43°C on T2w planning MRI:



Maximum Temperature 52-55°C on acute post-treatment CE-MRI:





- Pre-clinical trials: “acute cell kill” zone = contrast enhancement zone in the periphery of non-perfused volume (NPV)

TEMPERATURE CONTROL

	PARAMETER	AVERAGE (n=30)	95% CI (n=30)	RANGE (n=30)
	Prostate Volume (cc)	47 cc	41 – 54	21 – 95
	Treatment Time (min)	36 min	32 – 40	24 – 61
Linear	Targeting Accuracy (mm)	0.1 mm	-0.1 – 0.2	-0.6 – 1.1
Linear	Targeting Precision (mm)	1.3 mm	1.2 – 1.5	0.7 – 2.4
Volume	Over-Targeted Volume (cc)	0.8 cc	0.6 – 1.0	0.1 – 2.6
Volume	Under-Targeted Volume (cc)	1.0 cc	0.6 – 1.4	0.0 – 4.8
	Dice Similarity Coefficient (DSC)	0.94	0.93 – 0.94	0.91 – 0.96

SAFETY OVERVIEW

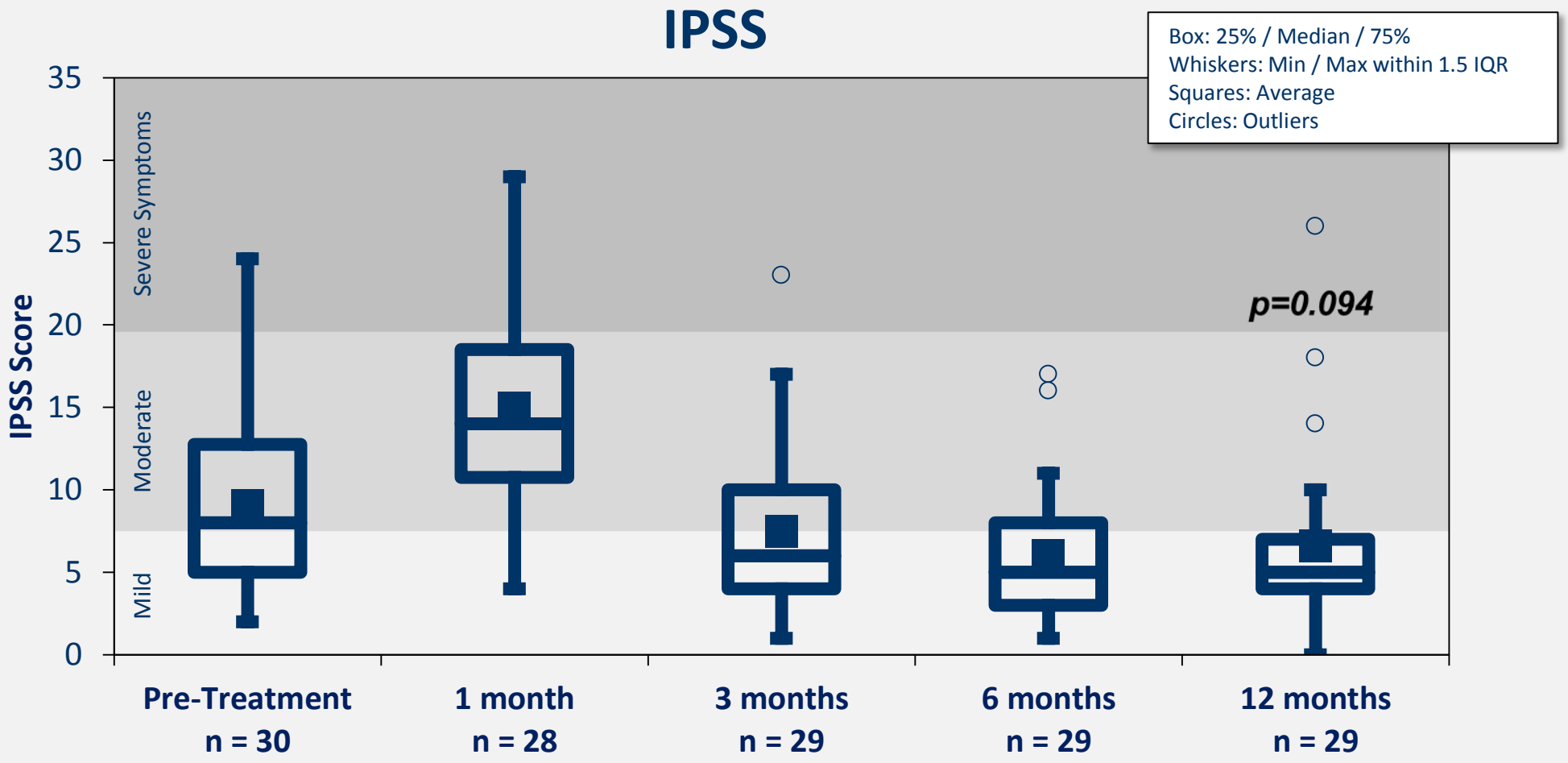
- No intraoperative complications
- No rectal injury or fistula
- No severe urinary incontinence
- No Grade 4 or higher adverse events
- Total of one attributable Grade 3 adverse event (epididymitis resolved with IV antibiotics)
- Majority are *acute* Grade 1 and 2 events related to GU system
- Estimated ED rate of 8% (IIEF item 2 ≥ 2)
- Planned overnight in hospital and discharged next day

ADVERSE EVENTS*

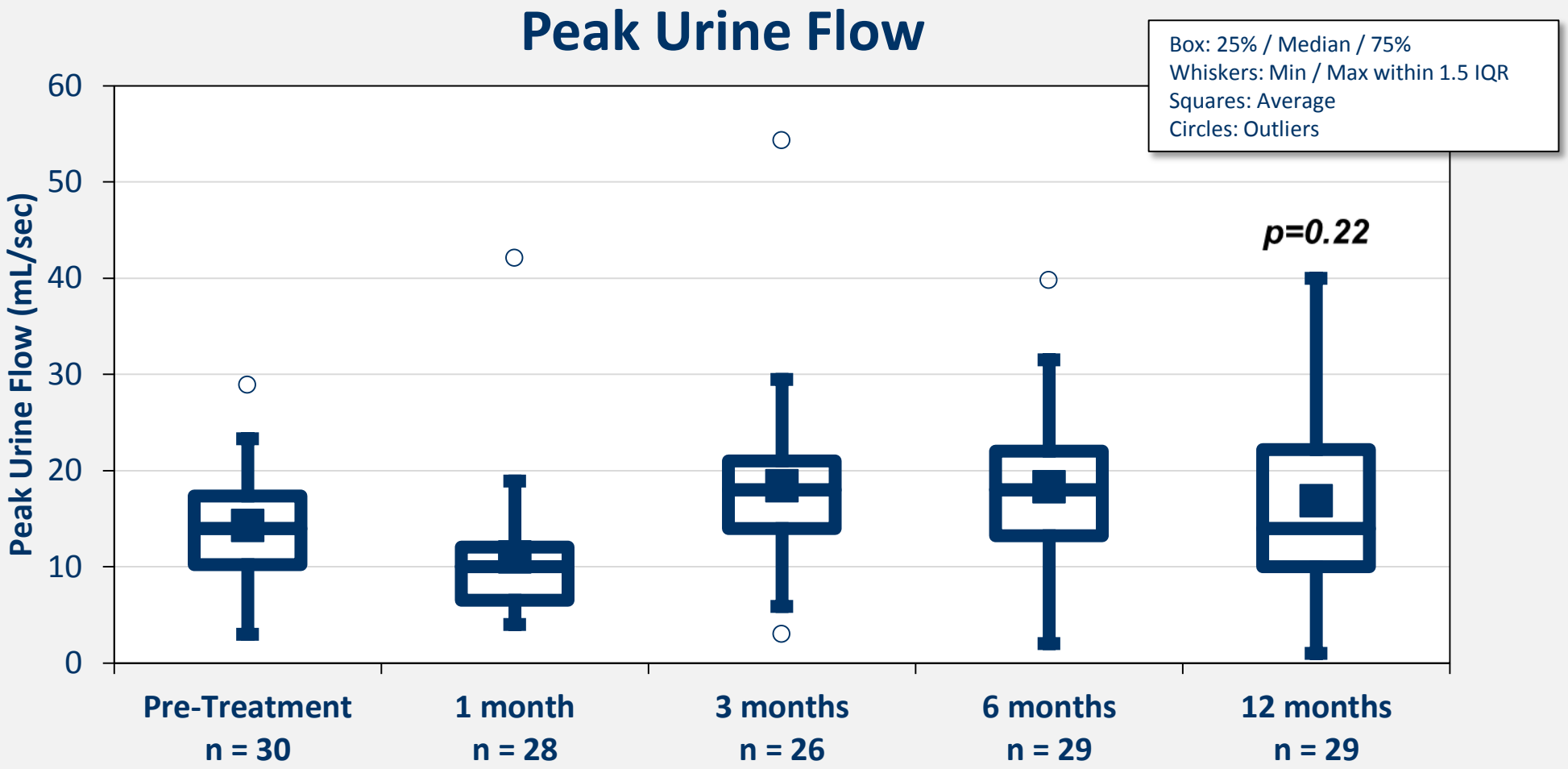
- Hematuria Grade 1 (13 patients) and G2 (2 patients), resolved
- Infections:
  - Urinary Tract Infection: G2 (10 patients), resolved with no action (1) or oral antibiotics (9)
  - Epididymitis: G3 (1 patient), resolved with IV-antibiotics
- Urinary retention:
  - G1 (3 patients) resolved spontaneously, repositioning SPC tubing or SPC irrigation
  - G2 (5 patients), resolved with medication (1) or prolonged-/re-catheterization (4)
- Urinary or urge incontinence:
  - G1 (1 patient), resolved with no action
  - G2 (3 patients), resolved with no action (1), resolved with medication (1), and ongoing (1) though downgraded to G1 and not using pads
- All GI-related events:
  - Bloating: G1 (3 patients), resolved with no action (may be due to anti-spasmodic drug)
  - Fecal straining: G1 (1 patient), resolved with no action after 7 days
  - Rectal pain: G1 (1 patient), resolved with no action after 1 day

* Related or possibly related adverse events: all G3 events shown, most severe/frequent G2 events shown, and select G1 events shown. Multiple of the same event are recorded once per patient using the highest grade.

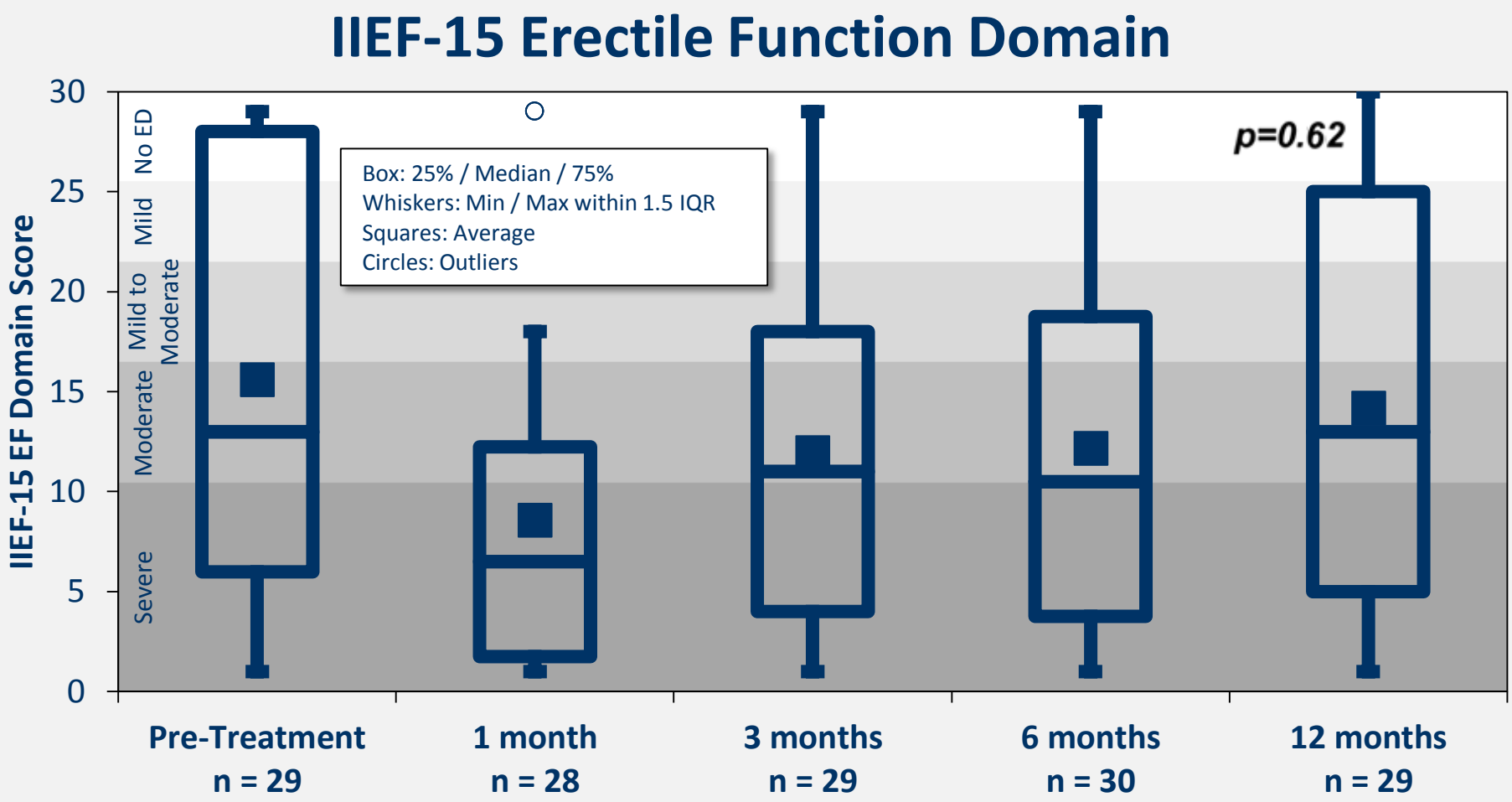
URINARY SYMPTOMS



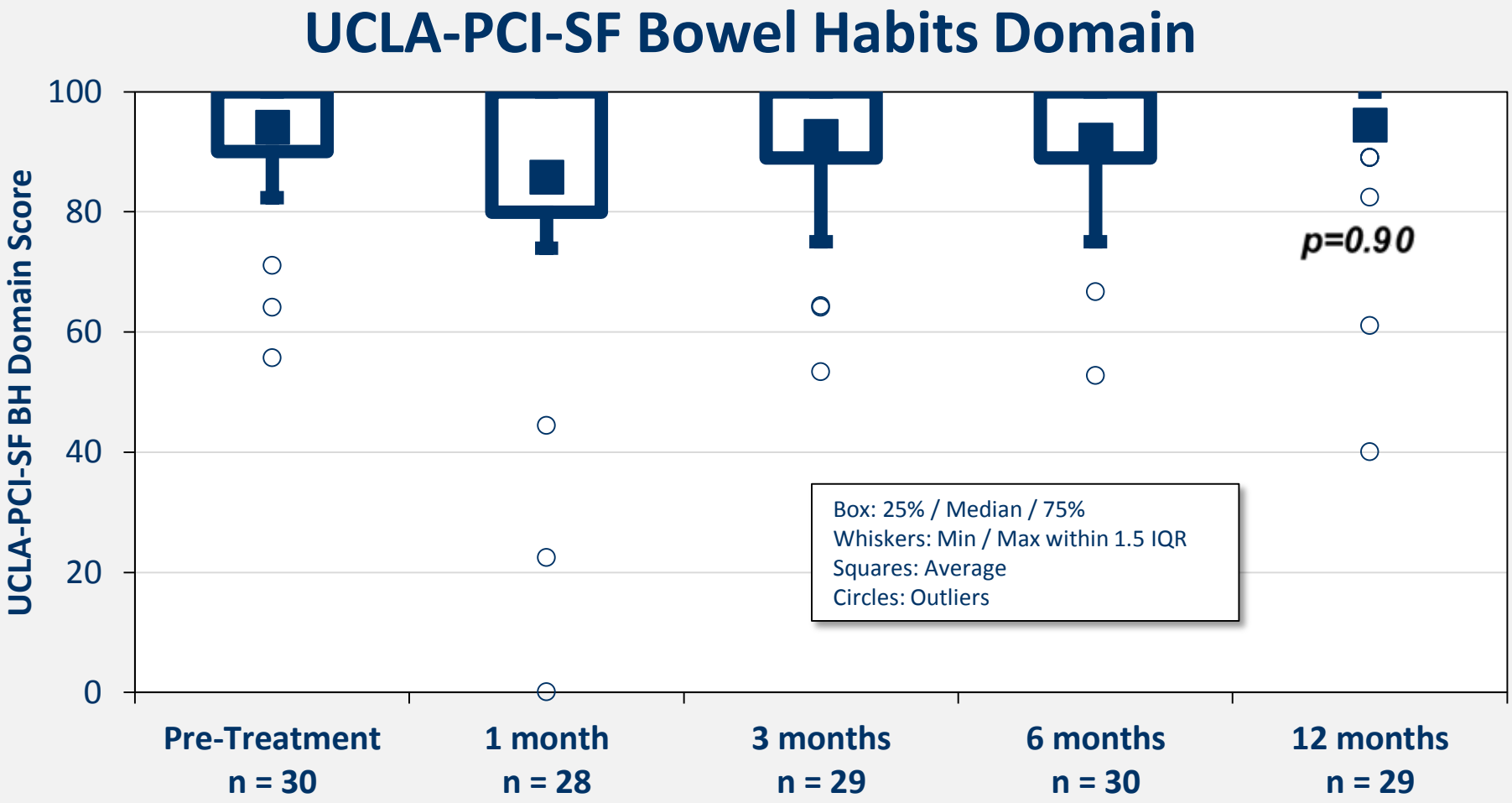
UROFLOWMETRY



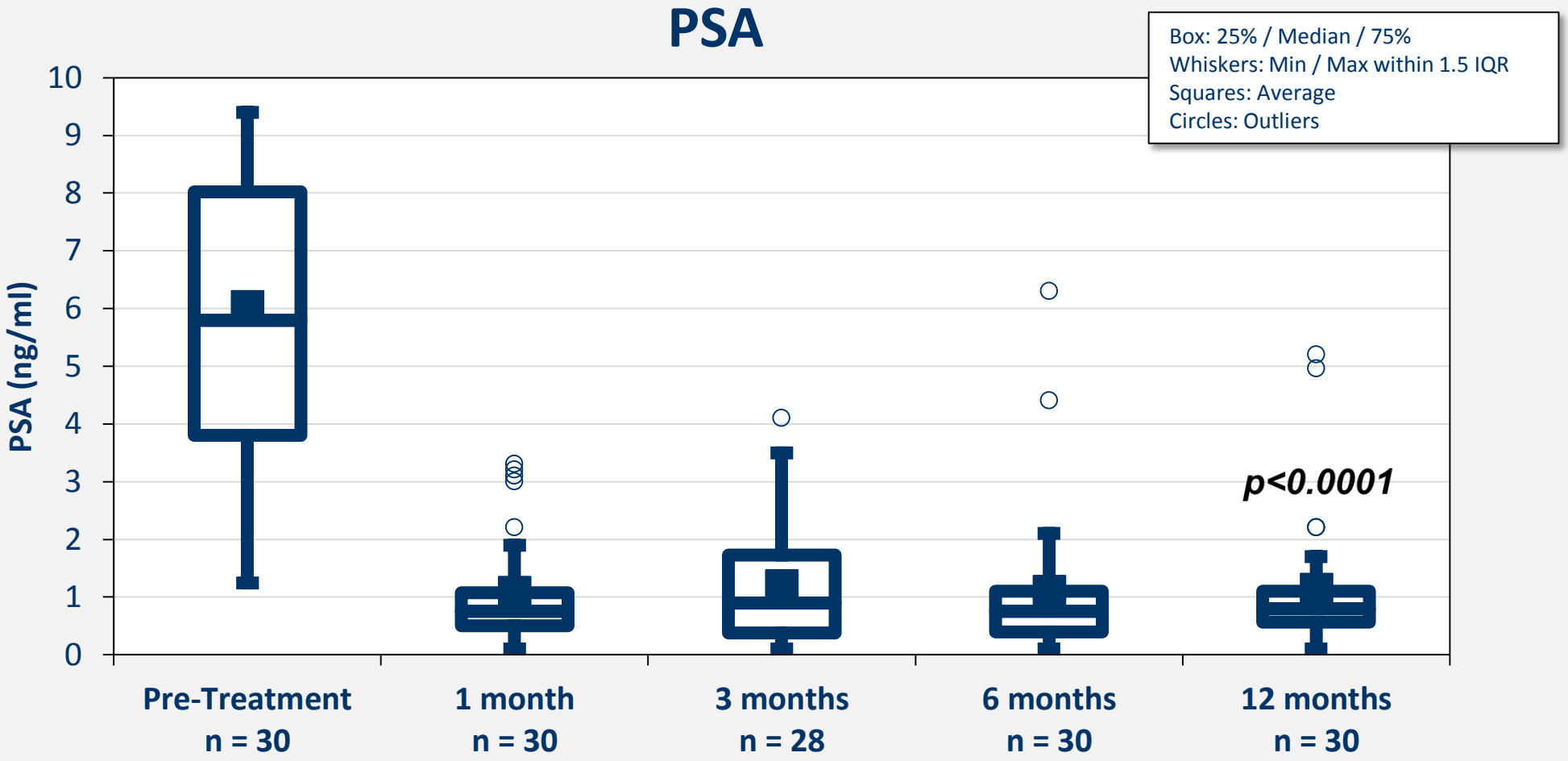
ERECTILE FUNCTION



BOWEL HABITS

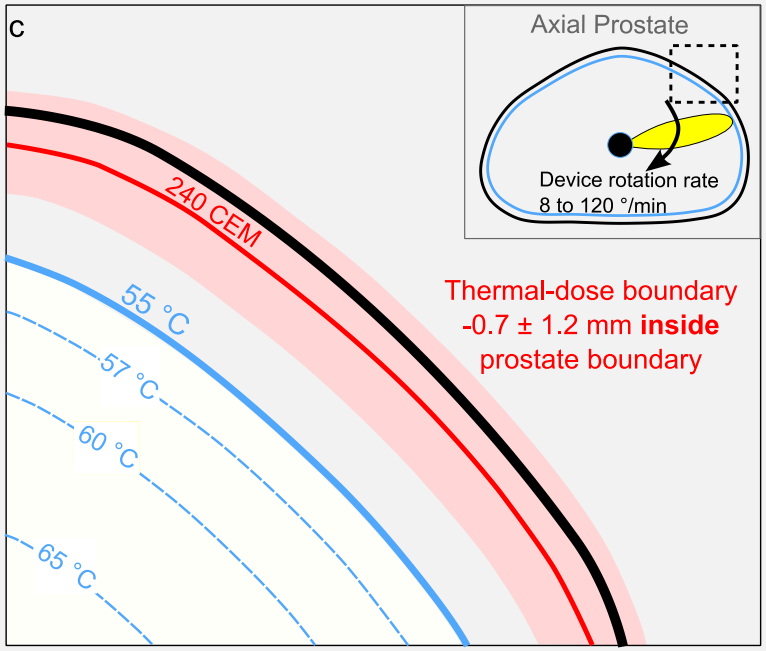


ABLATION EFFICACY



BIOPSY RESULTS AT 12 MONTHS

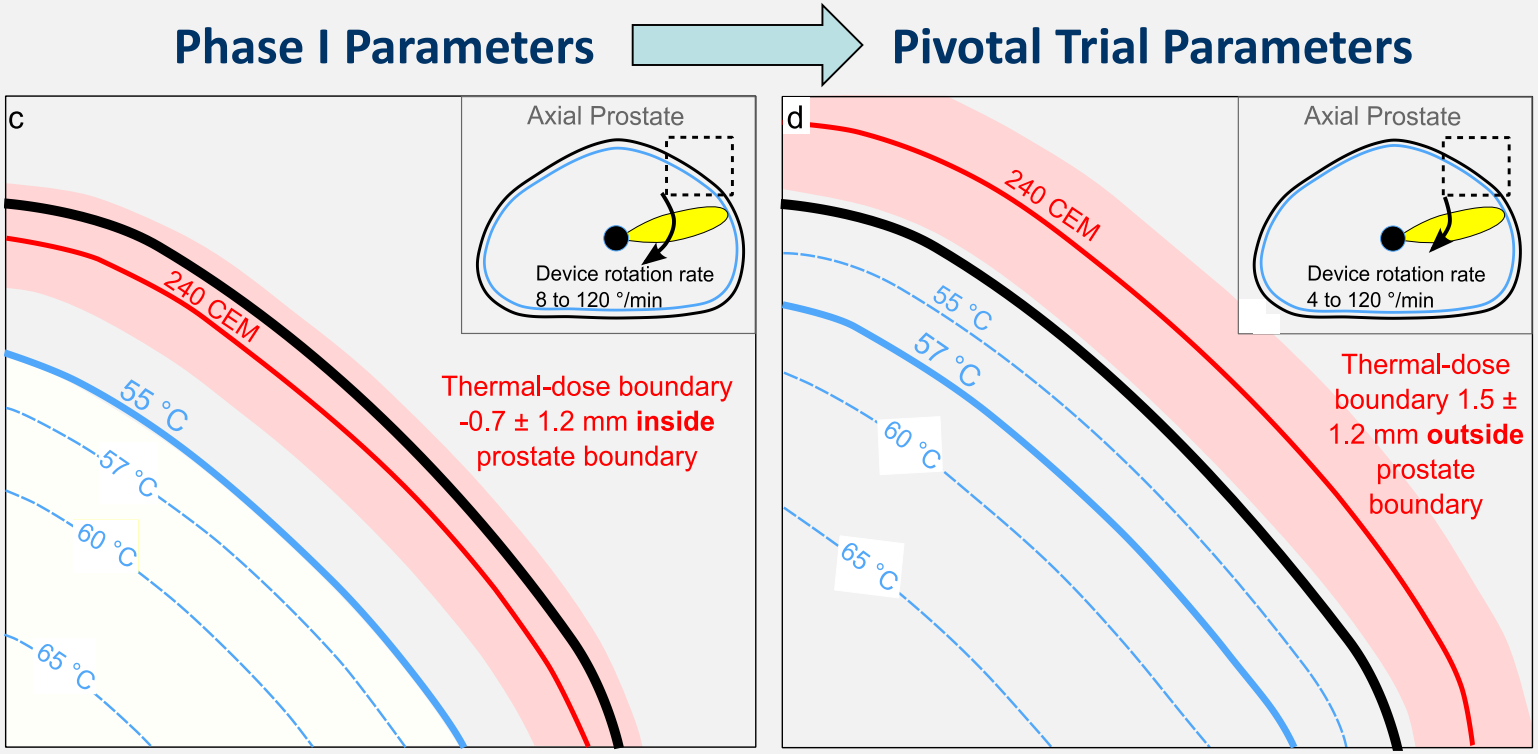
Phase I Treatment Parameters



- **Phase I** treatment parameters were **conservative**
  - First-in-human study as primary treatment for prostate cancer
  - Lethal thermal dose -0.7 ± 1.2 mm inside prostate
  - 10% viable prostate expected at prostate periphery
- MRI & TRUS biopsy show diminutive prostate volumes averaging 51% fibrosis (N=29)
- Positive biopsies demonstrate 61% reduction in total cancer length *(reduced cancer burden)*
- Positive biopsies –
  Clinically significant disease: 31% patients
  Any disease: 55% patients
- Patient status
  - 27 patients in active surveillance, no further treatment to date
  - 3 patients opted for active treatment (RPx, histology pending)

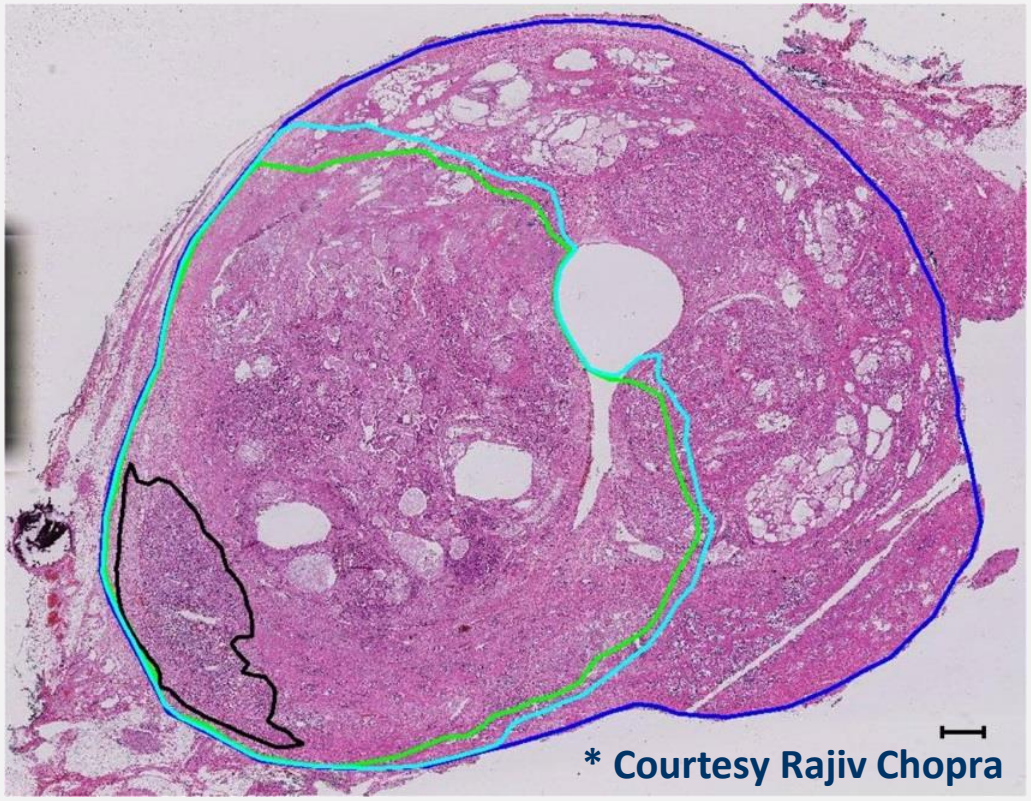
WHAT'S NEXT ?

- Pivotal clinical trial being initiated in larger prostate cancer population
- Reduced safety margin for complete whole-gland ablation



CLINICAL HISTOLOGY

Acute H&E Histology



Chopra *et al.* "Clinical Evaluation of Transurethral MR-HIFU for the Treatment of Localized Prostate Cancer," ISMRM Annual Meeting 2014 (Milan, Italy)

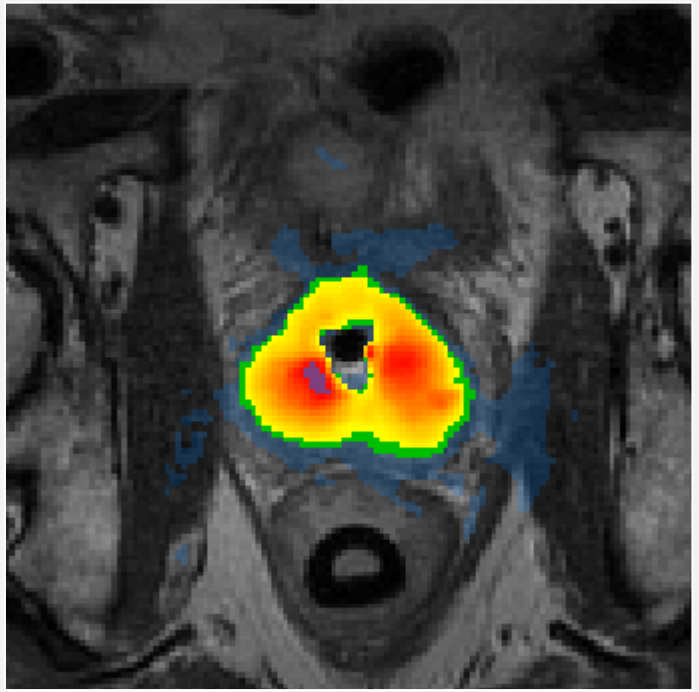
- Dr. Laurence Klotz, Dr. Masoom Haider & Dr. Rajiv Chopra at Sunnybrook Research Institute (Toronto ON, Canada)
- Second Phase 0 "Treat & Resect" study
- Targeted MRI-visible cancer for ablation, with pivotal trial treatment parameters
- Demonstrated complete cell kill (coagulative necrosis) to prostate boundary on acute H&E histology

Prostate Boundary
Acute Coagulative Necrosis
Outer Limit of Thermal Injury
Tumour

CONCLUSIONS

First Experience with TULSA-PRO

- Clinically Feasible
- Low toxicity & Good safety profile
- Ambulatory procedure
- Suitable to focal treatment
  - No MRI/TRUS fusion errors



What's next?

- Phase I follow-up to 5 years
- Pivotal trial to commence in 2016
- Endpoints: ablation efficacy, safety & biopsy
  - Reduced safety margins for complete whole-gland ablation
  - Diagnostic multi-parametric MRI