
# MR/US-Guided HIFU/FUS ablation of Prostate Cancer

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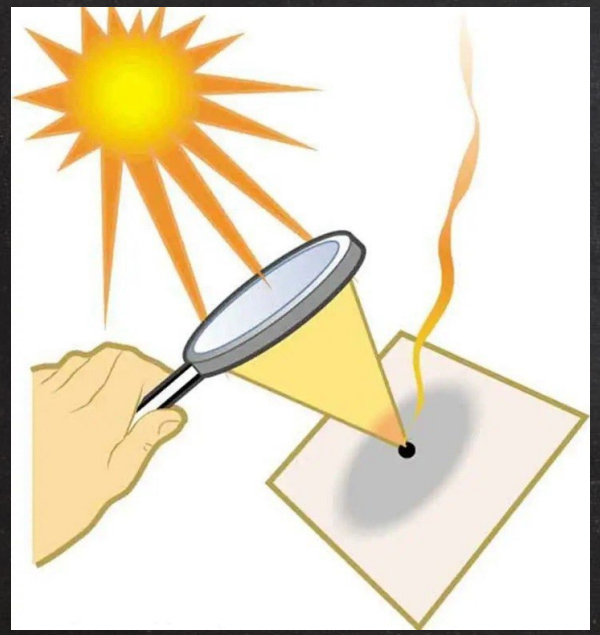
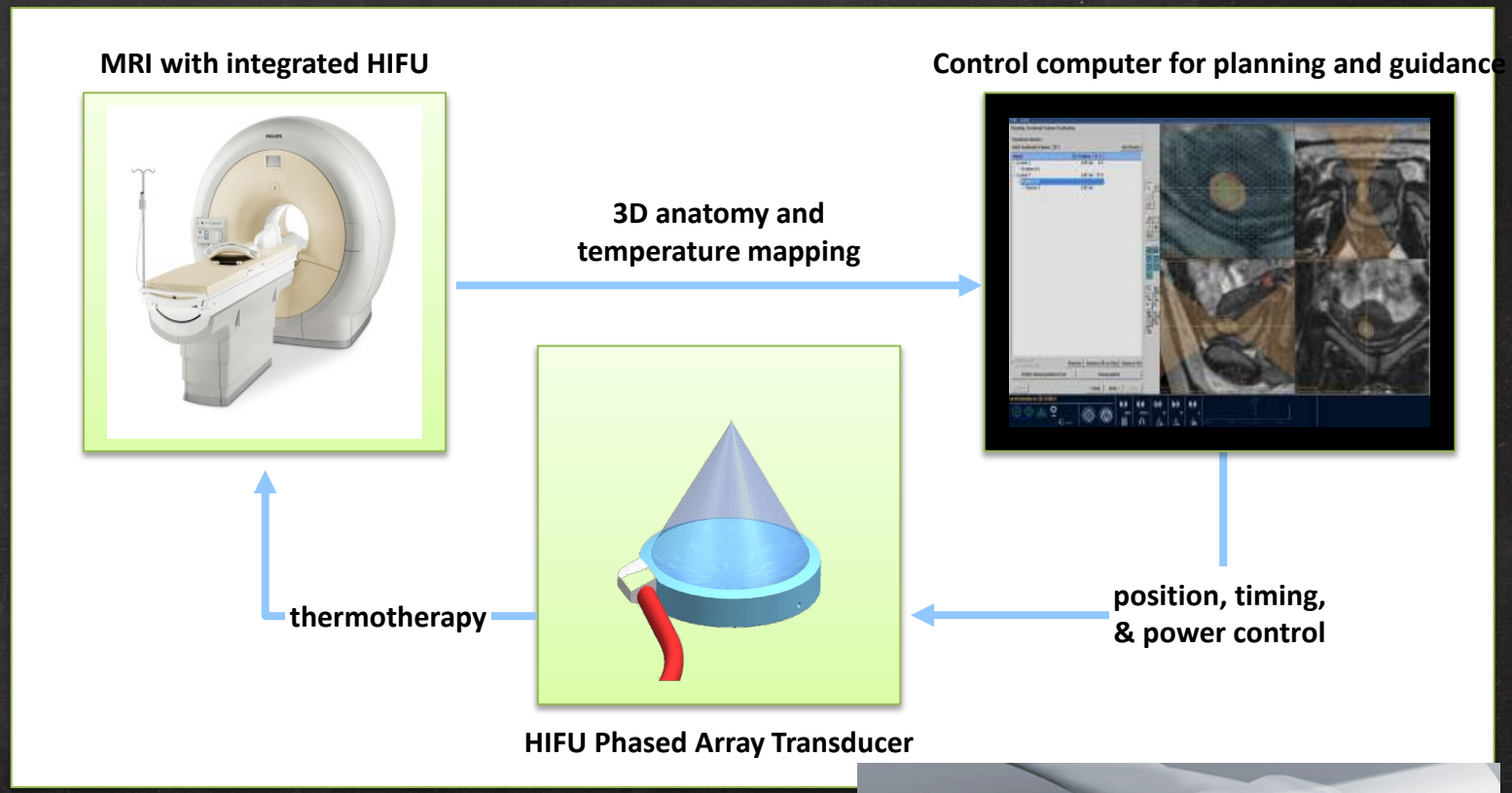
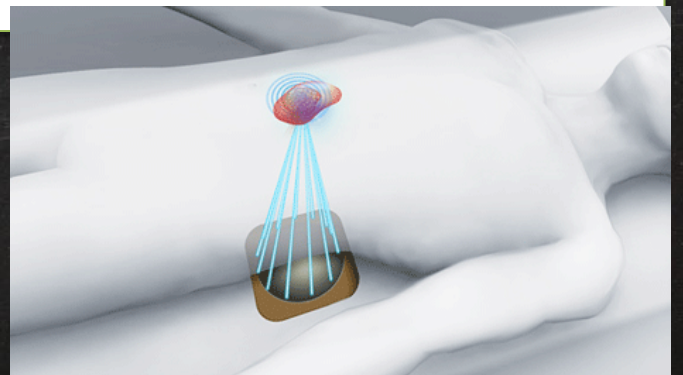
# FUS/HIFU

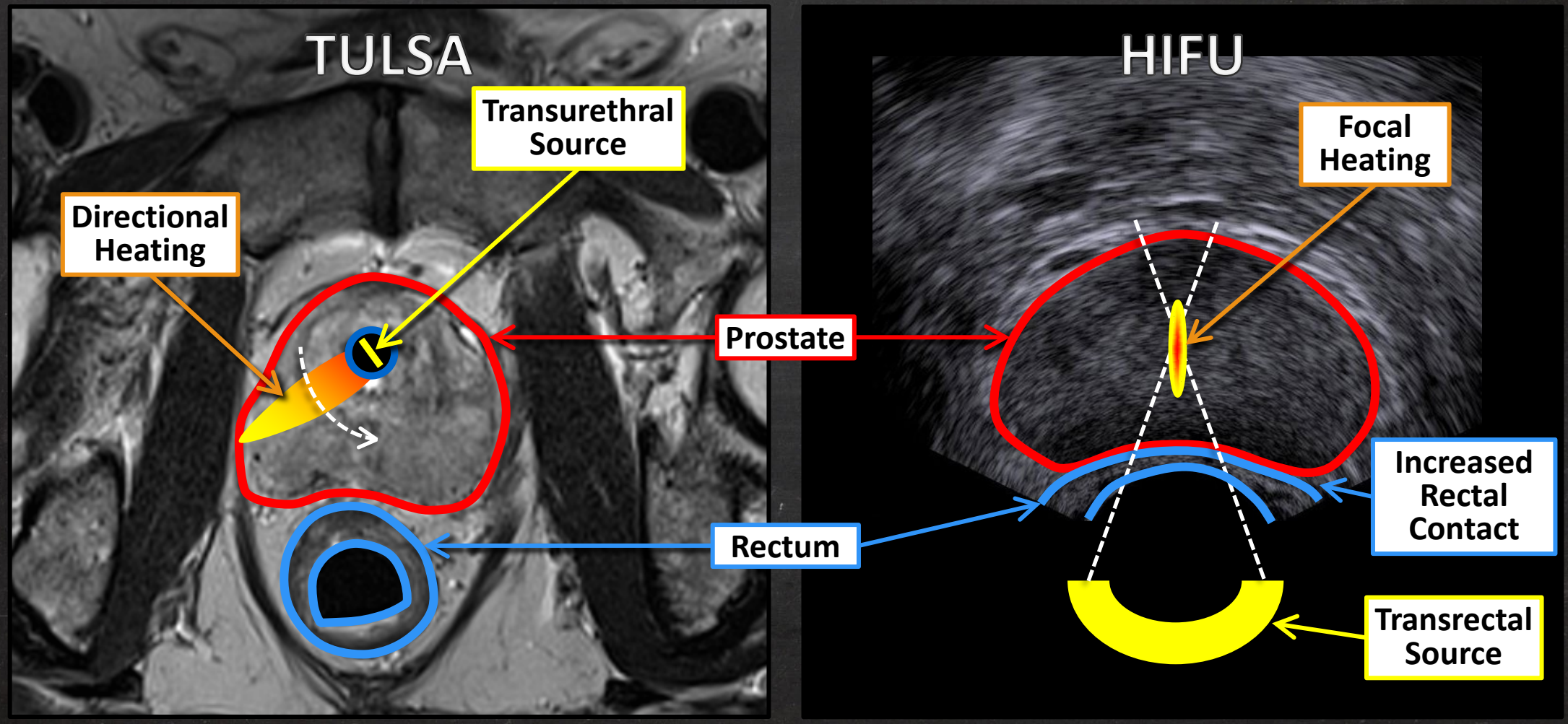
- HIFU: High-Intensity Focused ultrasound





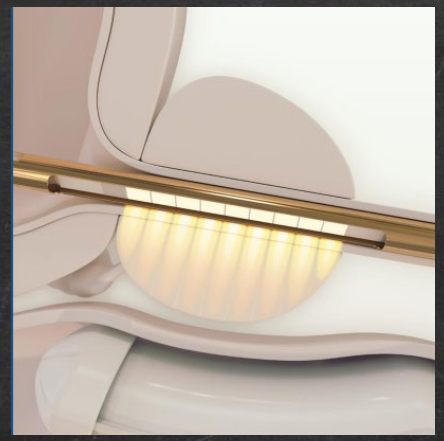
# FUS versus HIFU: Anatomy




* Images and overlays for illustrative purposes only

# FUS/HIFU

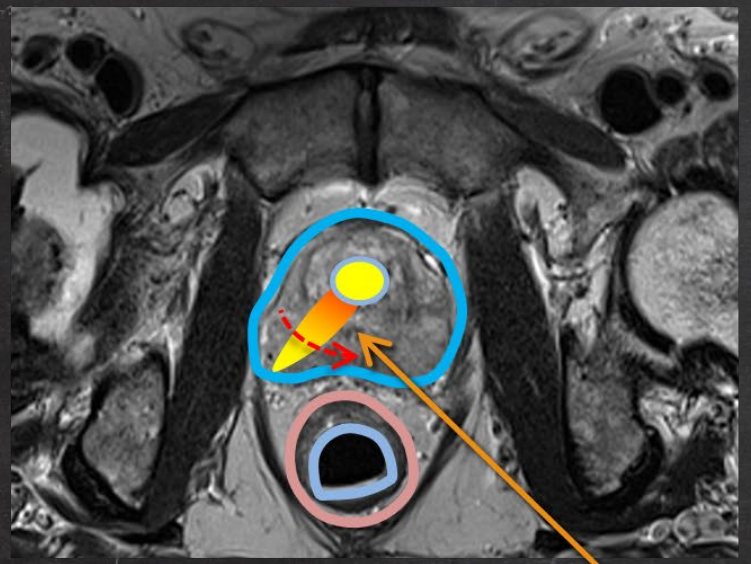
- FUS: 10  five mm Sonications

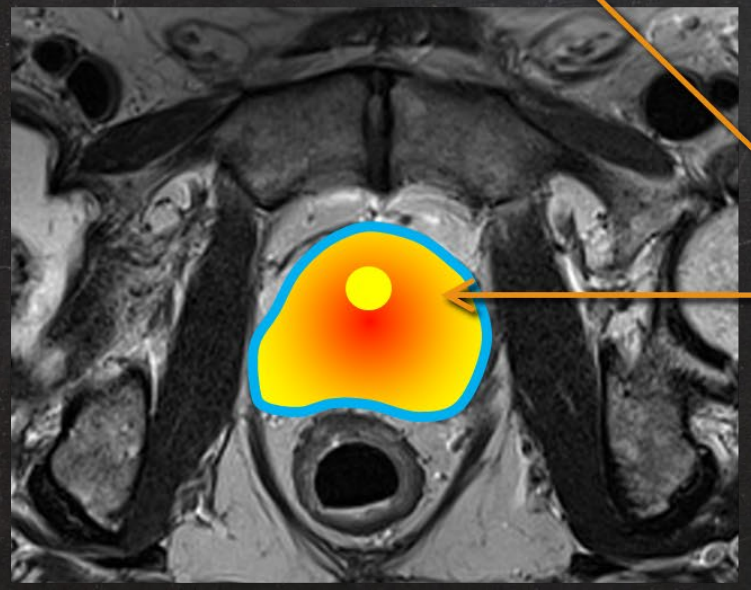


# MRI-Guided Transurethral Ultra-Sound Ablation (TULSA)

- Transurethral directional ultrasound
  - Incision-free, inside-out ablation
  - Sweeping ultrasound, continuous rotation (large, uniform ablation volumes)
  - Active cooling of urethra and rectum
- MRI-guided planning and robotic device positioning
- Real-time MRI thermal dosimetry and closed-loop ablation control
  - Delivers thermal therapy, measures temperature effect in real time, automatically adjusts the energy delivered

# TULSA vs. HIFU





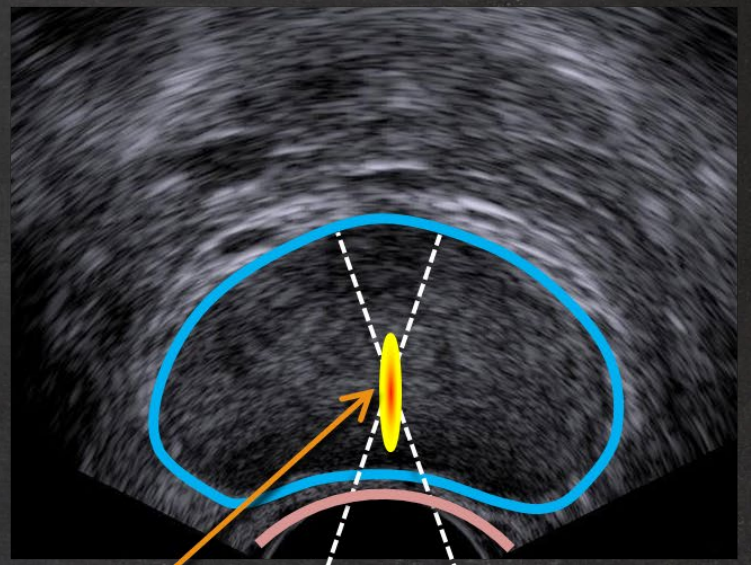
**Prostate**

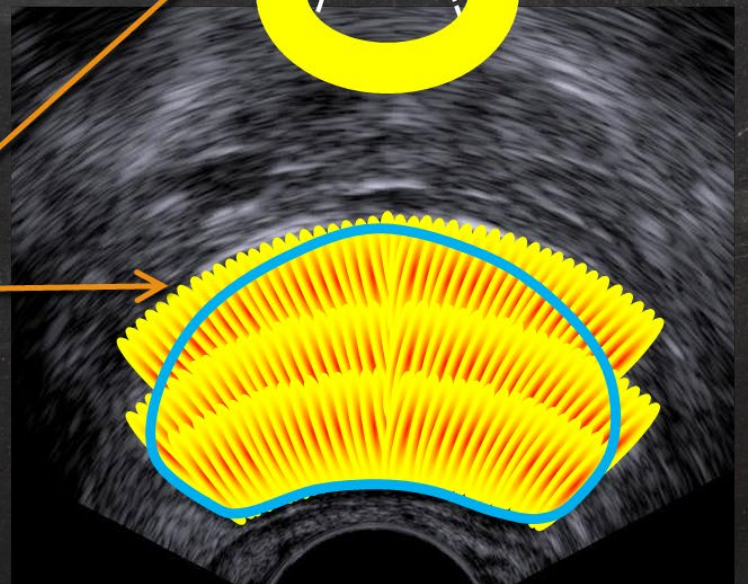
| Source Energy | |
|---|---|
| Trans-urethral | Trans-rectal |

| Cooling | |
|---|---|
| Yes | No |

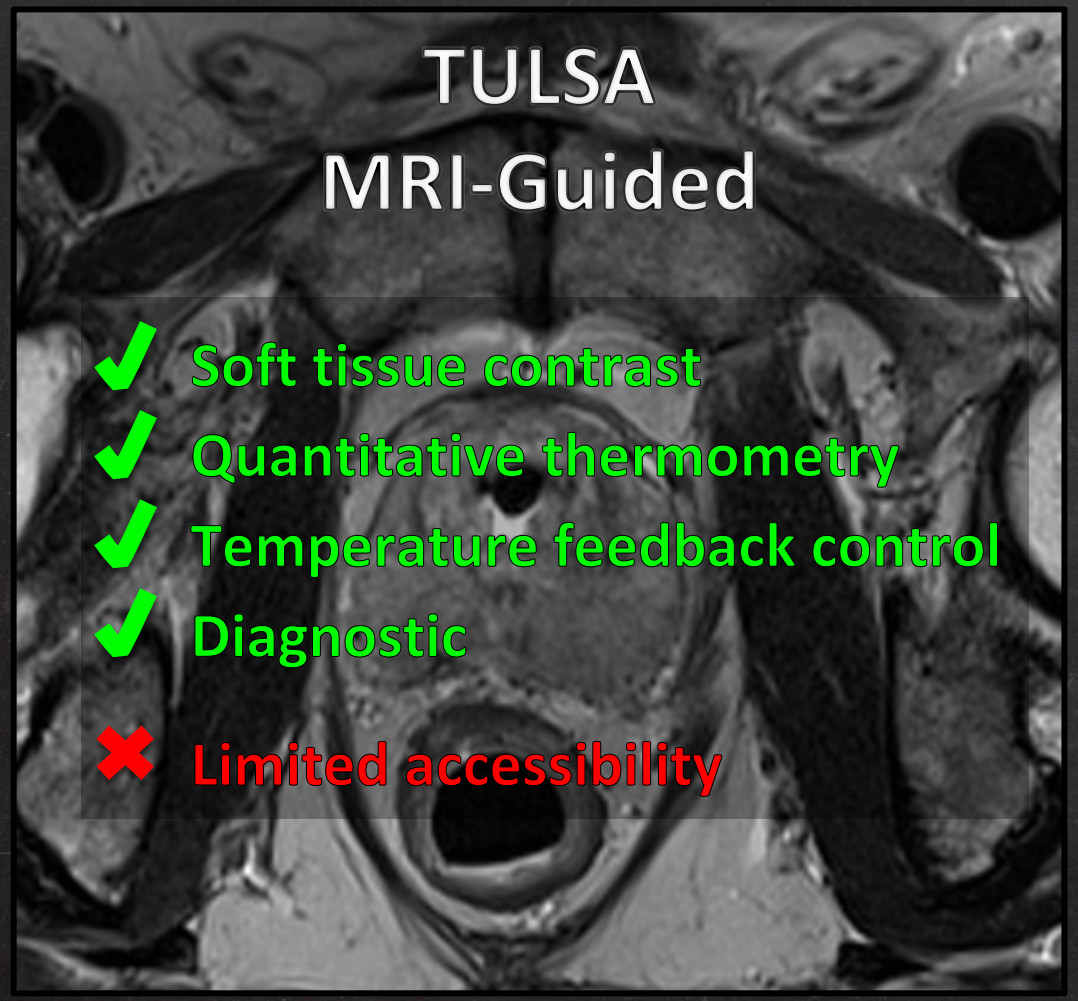
| Heating | |
|---|---|
| Directional | Focal |
| Continuous (Inside -> Out) | Discrete (Outside -> In) |

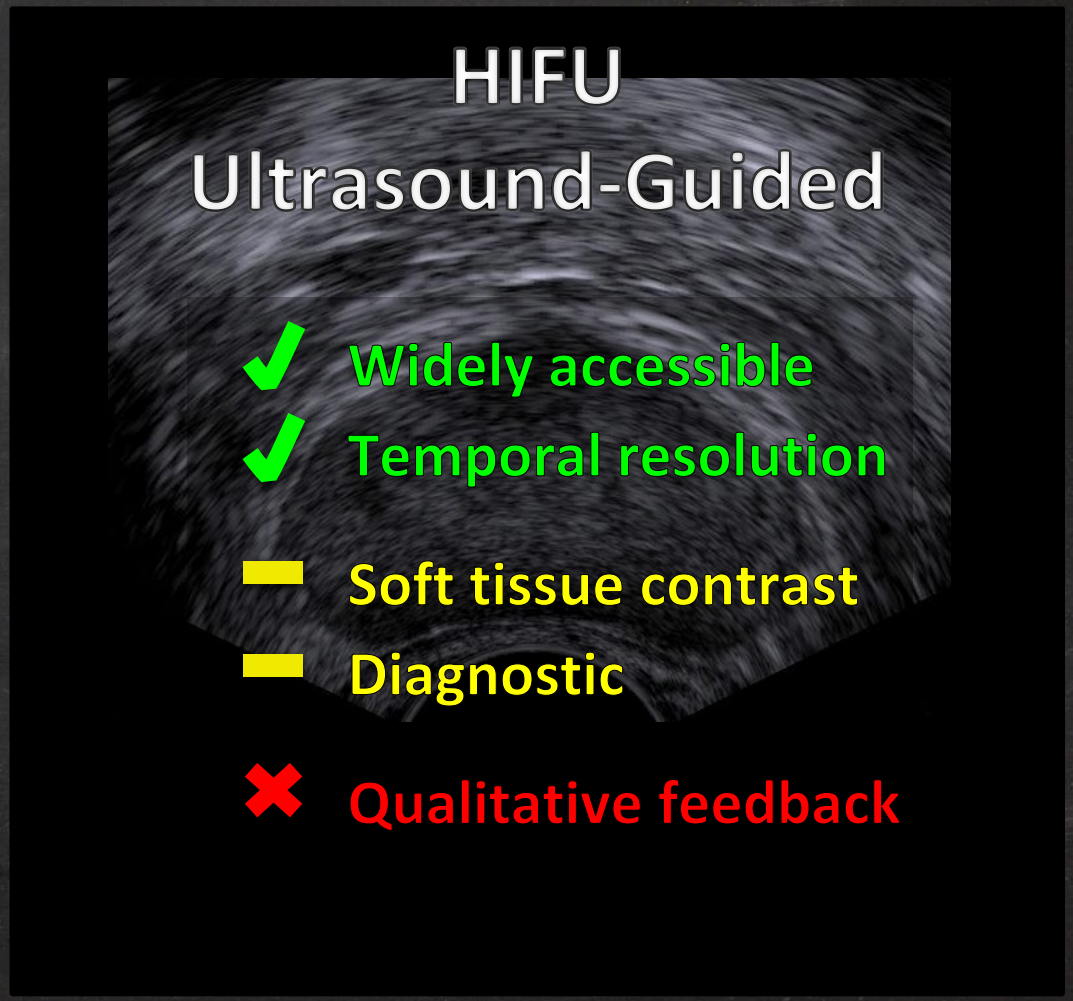
**Rectum**





# FUS versus HIFU: Imaging



# MRI-Guided Transurethral Ultra-Sound Ablation (TULSA) Technology

## Control Room

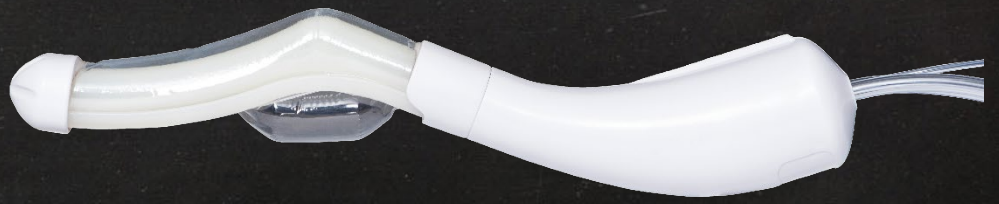
Treatment Delivery Console

- Fluid circuit for UA and ECD
- System electronics to power and control all system components

## MRI Room


**Ultrasound Applicator (UA)**


**Endorectal Cooling Device (ECD)**

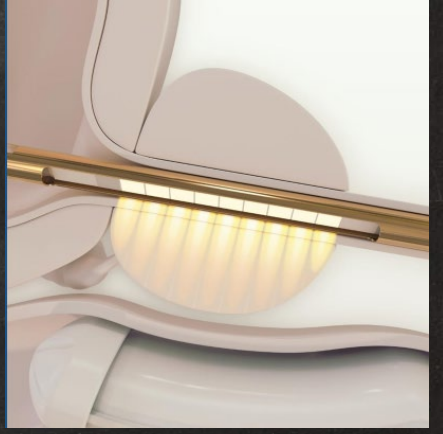


# SYSTEM COMPONENTS

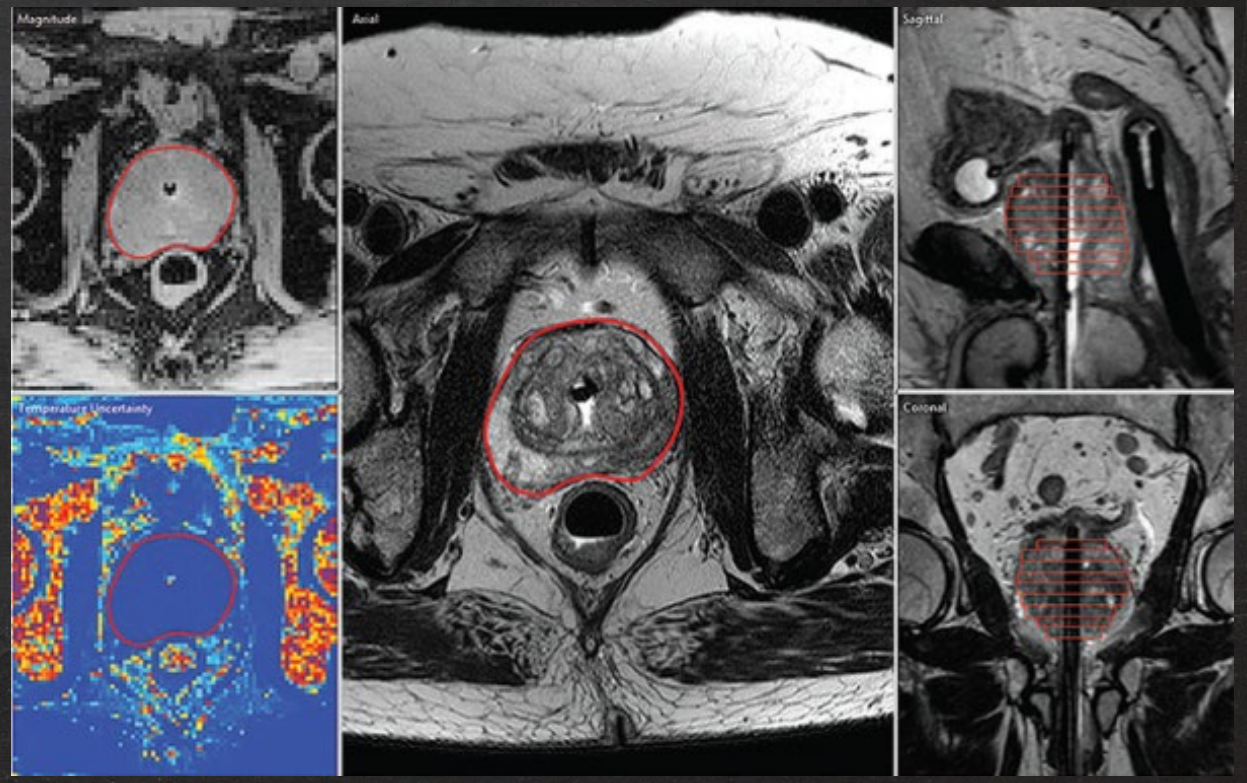
## Ultrasound Applicator (UA)


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

# FUS Technology



- With the patient in the MRI bore, physicians create 3D treatment plans using real-time visualization.
- Ablation using real time MRI imaging and thermometry



# TULSA MR Thermometry

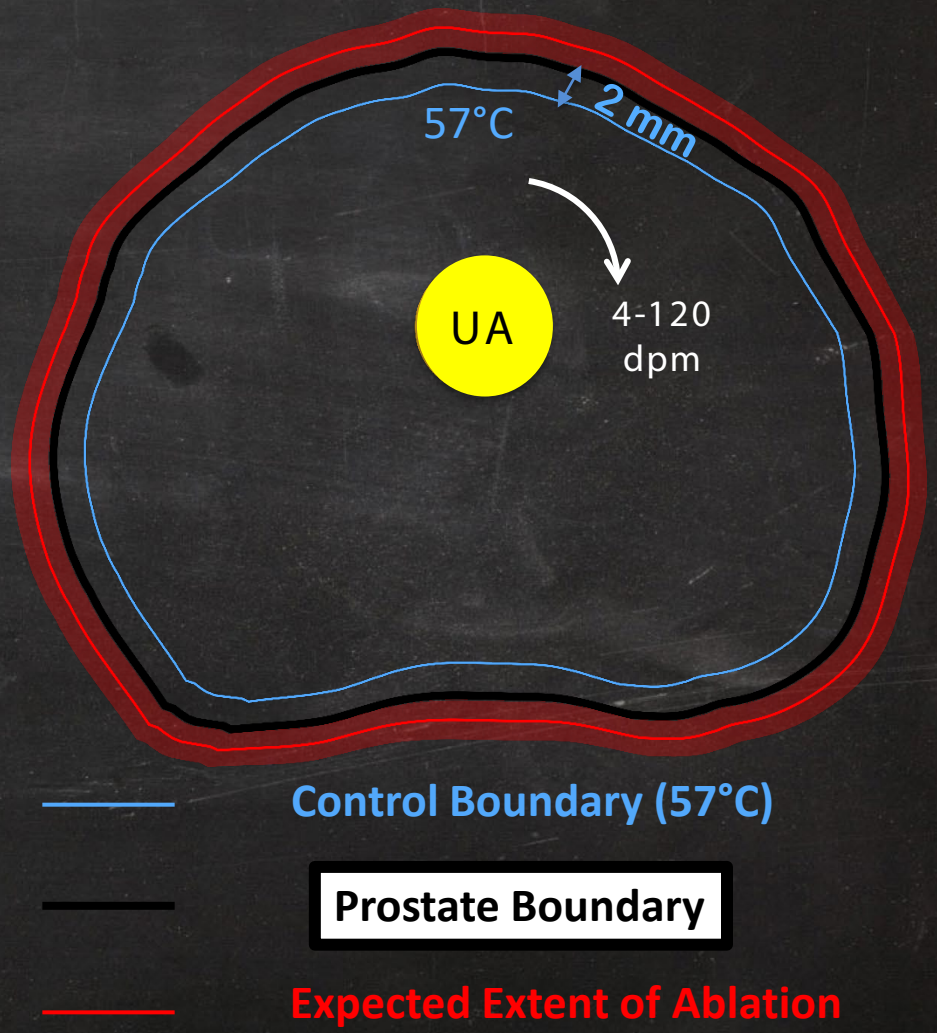
- UA power and rotation speed are controlled according to:
  - The real-time temperature at the control boundary

    (57°C within 2 mm of the prostate boundary)

  - The real-time maximum temperature within the monitoring margin

    (maintained below 86°C to avoid tissue boiling)

  - Possibility of boost to increase size with temperature



# TULSA MR Thermometry

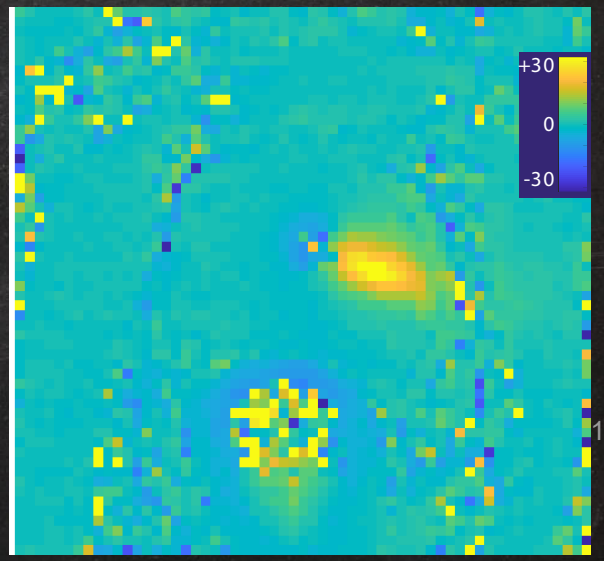
- Based on the Proton Resonance Frequency Shift Method
- Temperature difference is calculated from subtracted phase images

Phase 1
(Before Heating)

Phase 2
(During Heating)

Phase Difference

Temperature Map
(Temperature Difference [°C])



# TULSA MR Thermometry

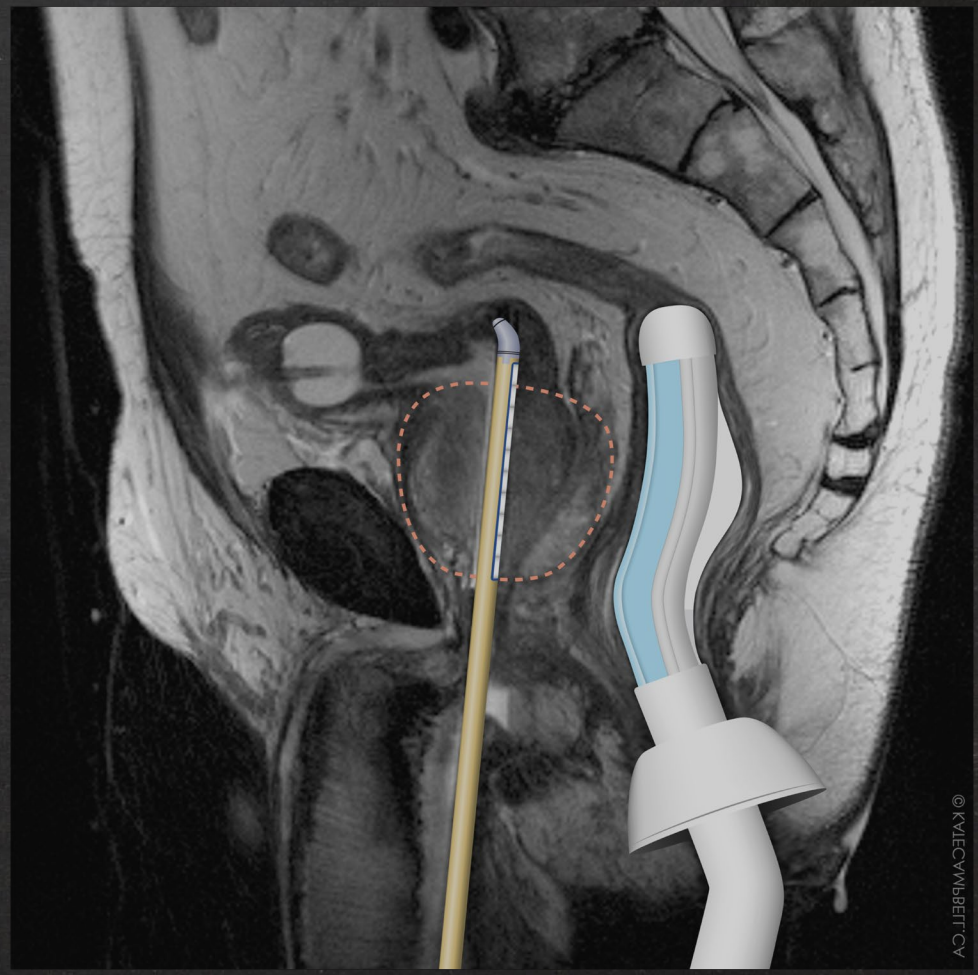
TULSA MR-Thermometry:

- is obtained with a relative measure, thus needing an external baseline temperature (i.e., patient's baseline temperature measured prior to starting the treatment)
- Is only valid in water-based tissues (not for fat tissue!)
- !! Does not distinguish temperature changes from motion (i.e., general anesthesia is required)

# INITIAL IMAGING

## Gross Device Positioning

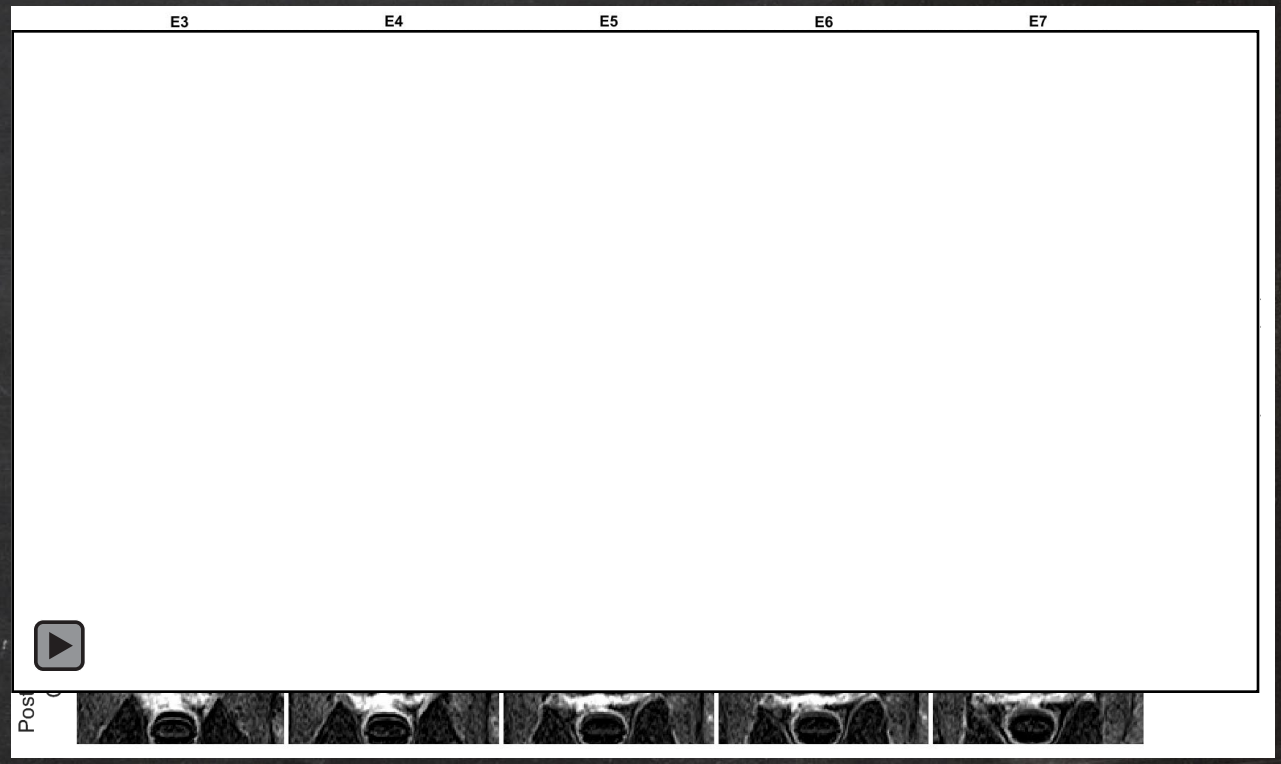
- Acquire gross positioning MR images (localizer / sag 2D) to determine the position of UA and ECD.
- Ensure UA is through the bladder neck.
- If there is air between ECD and anterior rectal wall, or if ECD is not facing prostate, manually adjust ECD and re-acquire images.



# DELIVERY

## Monitor Treatment Delivery

- Assess beam alignment, heating depth, artifacts, and patient motion
- Possibility of to deactivate elements, adjust UA beam angle, or edit boundary



# TULSA Indications

**Established**

- Whole-gland TULSA in patients with localized prostate cancer and:
  - Gleason Grade Group 1-2
  - Stage ≤ T2
  - PSA ≤ 15 ng/ml

**Within research protocols**

- Salvage treatment in biochemically (prostate-specific antigen higher than nadir or > 2 ng/ml) radio-recurrent prostate cancer
- Focal treatment in prostate cancer (T1-T2a; Gleason score ≤ 7; PSA < 15 ng/ml) patients being scheduled for radical prostatectomy
- Palliation of symptomatic locally advanced prostate cancer
- Treatment for large and symptomatic benign prostatic hypertrophy (BPH)

# TULSA Contraindications

**General**

- General contraindications to MRI
- Patients unfit for general anesthesia
- Large prostate calcifications along the US beam path
- Large prostate cysts along the control boundary
- Infections

**In patients needing radical prostate cancer ablation**

- Extracapsular tumor extension
- Metastases
- Tumour within 3-mm of the urethra or the external sphincter

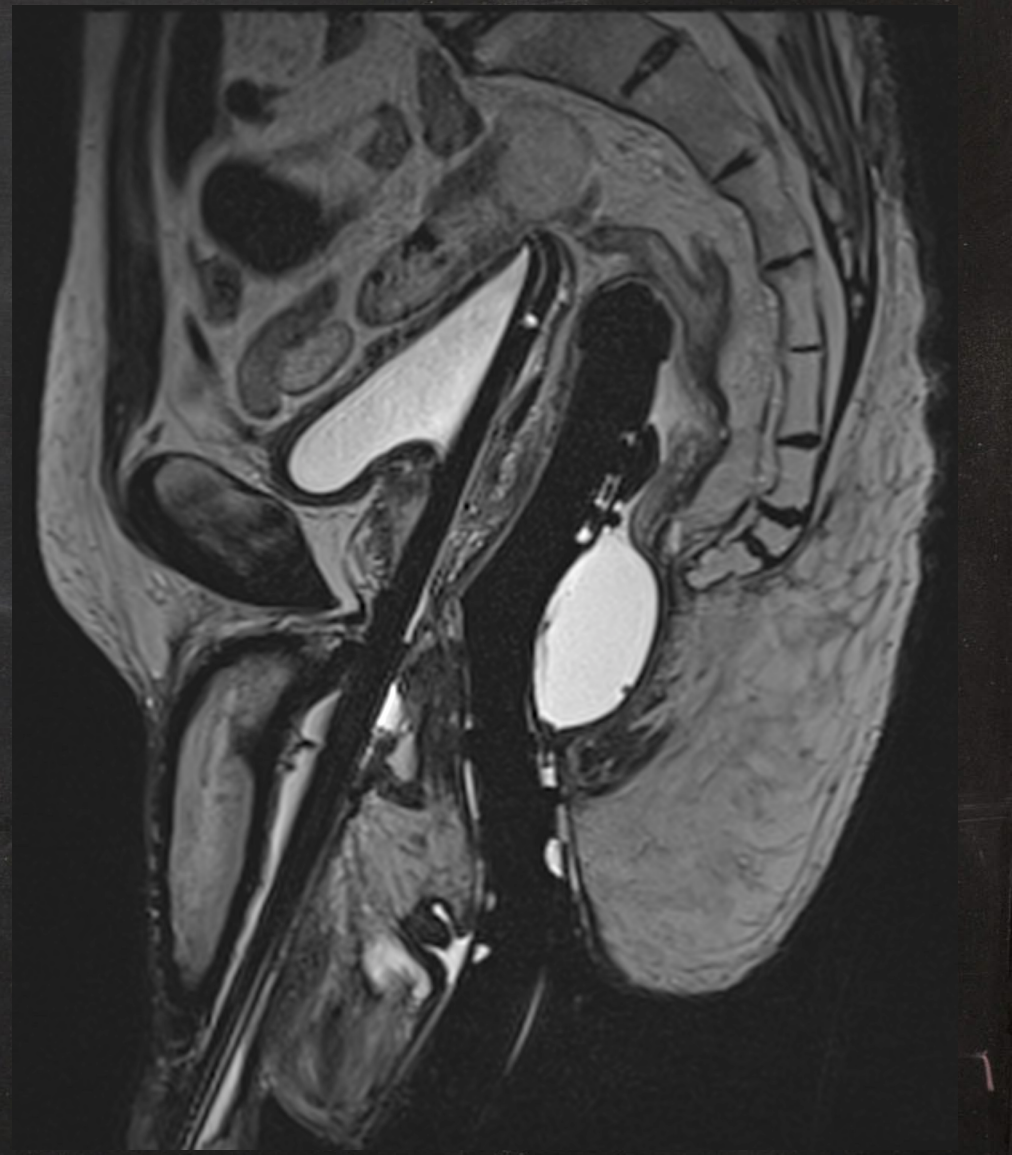
**In patients needing whole-gland treatment**

- Prostate sagittal length > 5.0 cm (For single segment treatment)
- Prostate axial diameter > 6.0 cm

# TULSA Step-by-step Workflow

## Step 1: Probe Positioning

- Acquire MR images (localizer / sag T2)
- Determine the position of UA and ECD
- Ensure UA is through the bladder neck
- If there is air between ECD and anterior rectal wall, or if ECD is not facing prostate, manually adjust ECD and confirm the new position with newly acquired images



# TULSA Step-by-step Workflow

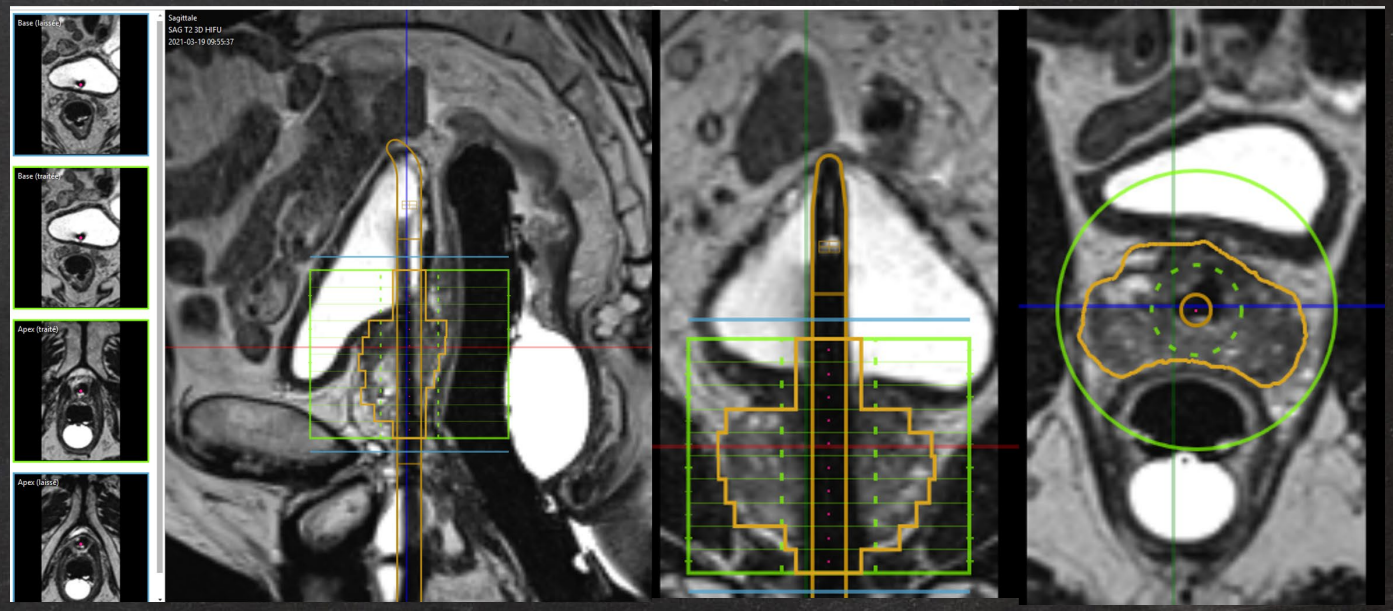
## Step 2: Device Registration

- Acquire & load 3D T2W images on TULSA MRI console
- Verify ECD and UA positioning in 3 planes
- Align graphical representation of the UA to the actual UA displayed on the MRI images

# TULSA Step-by-step Workflow

## Step 3: Define UA Treatment Location (Coarse)

- Move UA overlay to align the treatable volume with target tissue, and avoid critical structures (external urinary sphincter, bladder neck) from the treatment plan
- 4 mm safety overlay indicates tissue that are expected to be fully spared

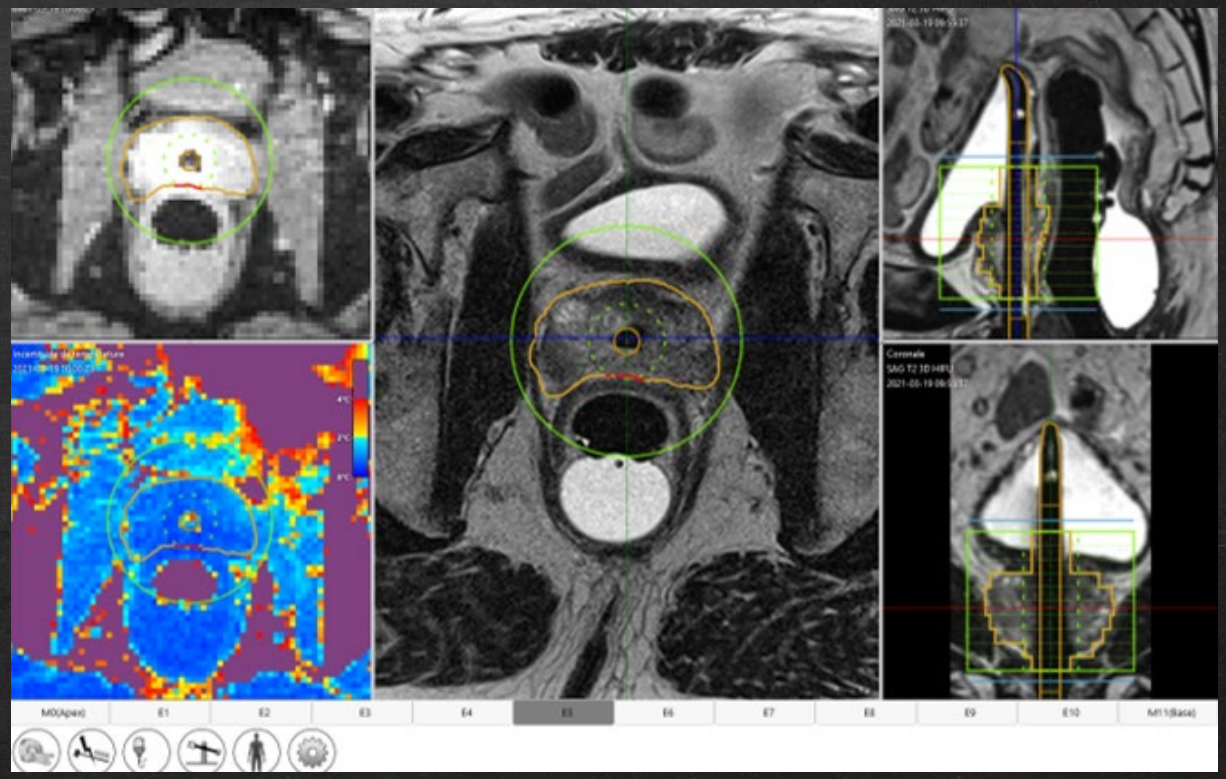



- The robotic positioning system automatically moves the UA along the linear axis to the desired treatment location and confirms the final position with newly acquired T2W MRI images

# TULSA Step-by-step Workflow

## Step 4: Treatment Boundaries and Thermometry Quality

- Acquire thermometry images aligned to UA elements
- Acquire and open Ax T2W images aligned to UA elements
- Adjust for distortion between thermometry and T2W images
- Contour targeted prostate tissue for each active US element



# TULSA Step-by-step Workflow

## Step 5: Energy Delivery

- Define direction of UA rotation and move UA to the desired starting angle
- Input patient's body temperature and start the treatment

# TULSA Step-by-step Workflow

## Step 6: Monitor Treatment

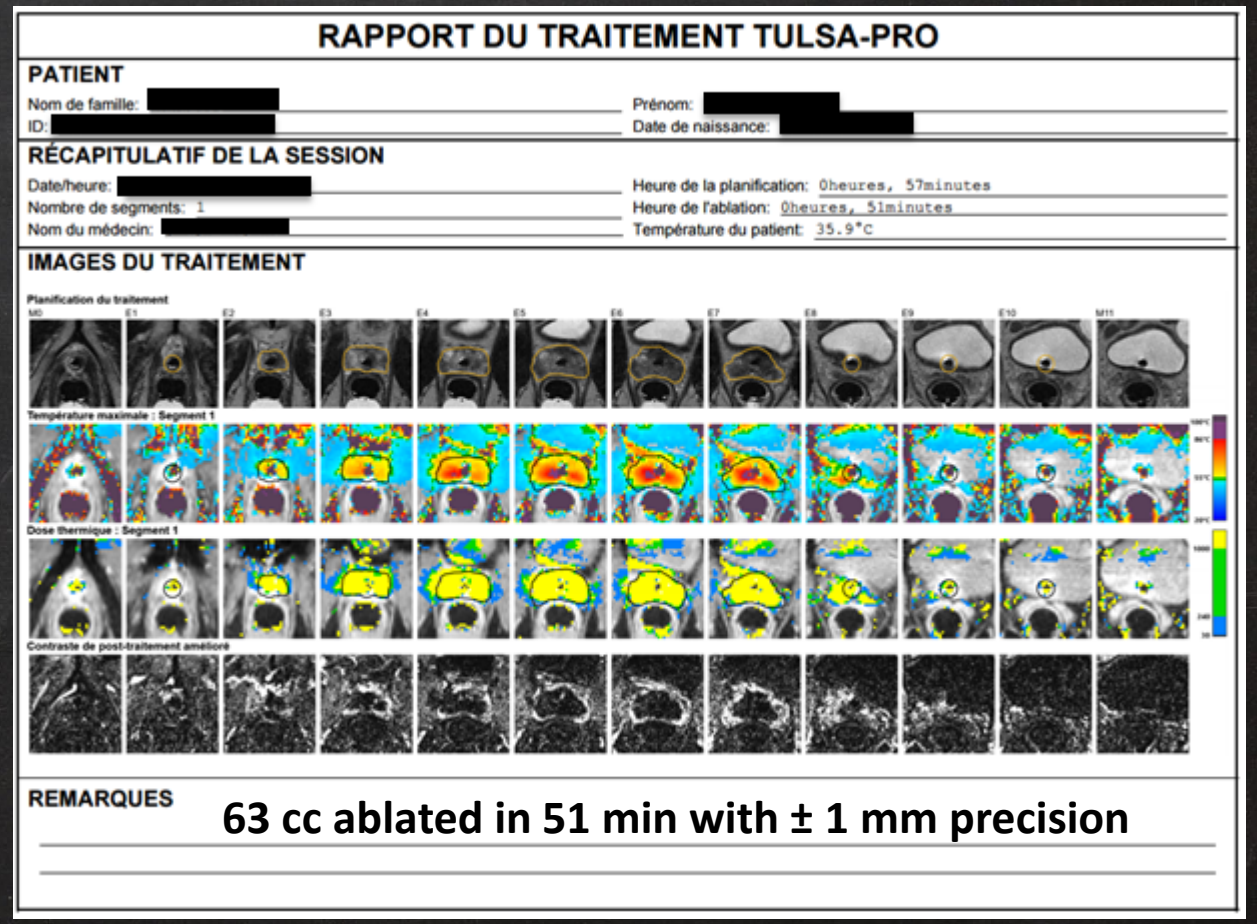
- Pause if patient motion is suspected
- If necessary, deactivate elements, adjust UA beam angle, or edit boundary

- ***Current*** – *color map* of most recent temperature image
- ***Max*** – *color map* of maximum temperature from start of treatment
- ***Motion*** – *difference* between most recent magnitude and first reference
- ***Anatomy*** – most recent magnitude image
- ***Planning*** – most recent AX T2 (not real-time)
- ***Dose*** – colormap of cumulative thermal dose

# TULSA Step-by-step Workflow

## Step 7: Treatment Confirmation and Report

- Acquire post-treatment Ax T1 pre-Gd MR images with UA and ECD in place
- Administer Gd I.V. and acquire post-Gd images to assess the extension of the treated area
- Create a final report of the treatment



**RAPPORT DU TRAITEMENT TULSA-PRO**

**PATIENT**

Nom de famille: [redacted] Prénom: [redacted]

ID: [redacted] Date de naissance: [redacted]

**RÉCAPITULATIF DE LA SESSION**

Date/heure: [redacted] Heure de la planification: 0heures, 57minutes

Nombre de segments: 1 Heure de l'ablation: 0heures, 51minutes

Nom du médecin: [redacted] Température du patient: 35.9°C

**IMAGES DU TRAITEMENT**

Planification du traitement

Température maximale : Segment 1

Dose thermique : Segment 1

Contraste de post-traitement amélioré

**REMARQUES**

**63 cc ablated in 51 min with ± 1 mm precision**

# Summary of TULSA Literature

| Study | Objective | Design | Inclusion criteria | N. Patients | Oncologic & Functional Results | Complications |
|---|---|---|---|---|---|---|
| Klotz et al, J Urol 2021 | 12-mo safety and efficacy of whole-gland TULSA ablation of prostate cancer | Prospective, multi-center, single-arm pivotal | • Age 45 to 80 years<br>• Gleason Grade Group 1-2<br>• Clinical stage ≤T2b<br>• PSA ≤15 ng/ml<br>• Minimum 10-core biopsy<br>• No previous treatment | 115 (median age 65 years) | • PSA reduction ≥75%: 96% (110/115 patients)<br>• Median PSA reduction of 95% and nadir of 0.34 ng/ml<br>• 72/111 (65%) patients: no evidence of cancer at 12-month biopsy<br>• Erections maintained or regained in 69/92 (75%) patients | • 4%: genitourinary infections<br>• 2%: urethral stricture<br>• 1.7%: urinary retention<br>• 1%: urethral calculus<br>• 1%: pain<br>• 1%: urinoma |
| Lumiani et al, J Urologic Oncology 2021 | Primarily, partial gland ablation of localized prostate cancer with neurovascular bundle sparing possibility | Retrospective, single-center, single-arm study | • Age 63 to 76 years<br>• Low- to high-risk localized prostate cancer or recurrent cancer<br>• PI-RADS ≥ 3<br>• No calcification ≥ 5 mm<br>• No contraindications to MRI and/or general anesthesia | 52 (median age 67 years) | • Median PSA reduction of 86.25% and nadir of 1.1 ng/ml<br>• Early treatment success rate of 88%<br>• 9/14 total recurrences had positive biopsy for clinically significant cancer between 9-24 mo<br>• LUTS improvements in 83% of patients<br>• 98% maintained pad-free urinary continence | • 25% Clavien-Dindo Grade I<br>• 3.8% Clavien-Dindo Grade IIIa<br>• No Grade IIIb or higher |
| Viitala et al, BJU International 2021 | Safety and feasibility of TULSA for the treatment of benign prostatic obstruction (BPO) | Investigator-initiated, prospective, non-randomized, single-arm, single-center Phase-I | • Men with symptomatic BPO previously scheduled for primary TURP<br>• No cancer evidence<br>• No calcification ≥ 10 mm<br>• No contraindications to MRI and/or general anesthesia | 10 (median age 68 years) | • Median prostate volume and PSA reduction at 12 months of 33% and 48%, respectively<br>• No changes in continence, sexual, erectile or bowel functions | • One Grade IIIb: epididymis abscess required drainage under general anesthesia<br>• One Grade II: UTI resolving with oral antibiotics<br>• 2 Grade I events |

# Summary of TULSA Literature

| Study | Objective | Design | Inclusion criteria | N. Patients | Oncologic & Functional Results | Complications |
|---|---|---|---|---|---|---|
| Anttinen et al, Eur Urol Open Sci 2020 | Safety and feasibility in radio-recurrent PCa | Prospective, single-center, phase I | • Men with localized, histopathologically verified, radio-recurrent Pca<br>• Phoenix-based BCR failure<br>• No contraindications to MRI and/or general anesthesia | 11 (median age 69 years) | • All 11 men received biopsy (4-6 cores) at 12-month post-TULSA<br>• 10/11 men free of any PCa in targeted ablation zone<br>• 2 out-of-field recurrences | • One Grade 3 AE<br>• Three Grade 2 AEs<br>• 4/11 UTI<br>• 3/11 UR (all 11 had ED at baseline)<br>• minimal change in IPSS, EPIC |
| Anttinen et al, Scandinavian Journal of Urology 2020 | Evaluation of the safety and feasibility of TULSA as palliative treatment for men with symptomatic locally advanced prostate cancer | Prospective, non-randomized, single-arm, single-center Phase-I | • Primary or radio-recurrent locally-advanced prostate cancer<br>• Life expectancy ≥ 3mo<br>• Ongoing/recurrent gross hematuria and/or urinary retention requiring continuous catheterization, which were not resolving by conservative or medical treatment | 10 (median age 76.5 years) | • 50% (5/10) patients: catheter-free at 1-week<br>• At last follow-up:<br>- catheter-free rate: 70% patients<br>- gross hematuria-free rate: 100% patients | • 30%: urinary tract infections |
| Bonekamp et al, Eur Radiol 2018 | Quantitative assessment of prostate volume reduction on 1 yr T2W MRI vs. post-treatment CE-MRI NPV | Retrospective subgroup analysis of prospective, multi-center cohort | • Age ≥ 65 years<br>• Gleason Grade Group 1-2<br>• Clinical stage ≤T2a<br>• PSA ≤10 ng/ml<br>• No previous treatment | 29 (median age 69 years) | • 88% reduction in viable prostate volume at 1 yr<br>• Immediate post-treatment NPV underestimates ablation | • No severe AEs |

# Summary of TULSA Literature

- 6 patients TULSA followed by robotic Prostatectomy 3 weeks after
- Lesion-targeted TULSA demonstrates accurate and safe ablation of PCa. TULSA achieved coagulation necrosis of all targeted tissues. A limitation of this treat-and-resect-study-design was conservative treatment near NVB in patients scheduled for RALP.

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ARTICLE

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**Feasibility of MRI-guided transurethral ultrasound for lesion-targeted ablation of prostate cancer**

Mikael Anttinen[a], Pietari Mäkelä[b], Visa Suomi[c], Aida Kiviniemi[b], Jani Saunavaara[c], Teija Sainio[c], Antero Horte[a], Lauri Eklund[d,e], Pekka Taimen[d,e], Roberto Blanco Sequeiros[b] and Peter J. Boström[a]

[a]Department of Urology, Turku University Hospital, Turku, Finland; [b]Department of Diagnostic Radiology, University of Turku, Turku, Finland; [c]Medical Imaging Centre of Southwest Finland, Turku University Hospital, Turku, Finland; [d]Institute of Biomedicine, University of Turku, Turku, Finland; [e]Department of Pathology, Turku University Hospital, Turku, Finland

ABSTRACT

**Background:** MRI-guided transurethral ultrasound ablation (TULSA) has been evaluated for organ-confined prostate cancer (PCa). The purpose of this study was to assess the safety and toxicity, accuracy and short-term evolution of cell-death after lesion-targeted TULSA.

**Methods:** This prospective, registered, Phase-I treat-and-3-week-resect-study enrolled six patients with MRI-visible-biopsy-concordant PCa. Lesions were targeted using TULSA with radical intent, except near neurovascular bundles (NVB). Robot-assisted-laparoscopic-prostatectomy (RALP) was performed at 3 weeks. Post-TULSA assessments included MRI (1 and 3 weeks), adverse events and quality-of-life (QoL) to 3 weeks, followed by RALP and whole-mount-histology. Treatment accuracy and demarcation of thermal injury were assessed using MRI and histology.

**Results:** Six patients (median age = 70 years, prostate volume = 60 ml, PSA = 8.9 ng/ml) with eight biopsy-confirmed MRI-lesions (PIRADS ≥3) were TULSA-treated without complications (median sonication and MRI-times of 17 and 117 min). Foley-catheter removal was uneventful at 2–3 days. Compared to baseline, no differences in QoL were noted at 3 weeks. During follow-up, MRI-derived non-perfused-volume covered ablated targets and increased 36% by 3 weeks, correlating with necrosis-area on histology. Mean histological demarcation between complete necrosis and outer-limit-of-thermal-injury was 1.7 ± 0.4 mm. Coagulation necrosis extended to capsule except near NVB, where 3 mm safety-margins were applied. RALPs were uncomplicated and histopathology showed no viable cancer within the ablated tumor-containing target.

**Conclusions:** Lesion-targeted TULSA demonstrates accurate and safe ablation of PCa. A significant increase of post-TULSA non-perfused-volume was observed during 3 weeks follow-up concordant with necrosis on histology. TULSA achieved coagulation necrosis of all targeted tissues. A limitation of this

ARTICLE HISTORY
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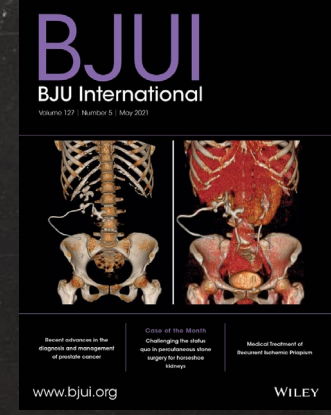
KEYWORDS
Focal therapy; lesion-targeted; prostate cancer; transurethral ultrasound ablation; MRI-guided; minimally-invasive; treat-and-resect

# Summary of TULSA Literature

- 3-year follow-up of a Phase I study of magnetic resonance imaging (MRI)-guided transurethral ultrasound ablation (TULSA) in 30 men with localised prostate cancer near whole-gland ablation, applying 3-mm margins sparing 10% of peripheral prostate tissue.
- Erectile function recovered by 1 year and was stable at 3 years. The PSA level decreased 95% to a median.
- Serial biopsies identified clinically significant disease in 10/29 men (34%) and any cancer in 17/29 (59%).
- By 3 years, seven men had recurrence (four histological, three biochemical) and had undergone salvage therapy without complications (including six prostatectomies




**Magnetic resonance imaging-guided transurethral ultrasound ablation in patients with localised prostate cancer: 3-year outcomes of a prospective Phase I study**

Shiva M. Nair[1], Gencay Hatiboglu[2], James Relle[3], Khalil Hetou[1], Jason Hafron[3], Christopher Harle[1], Zahra Kassam[1], Robert Staruch[4], Mathieu Burtnyk[4], David Bonekamp[2], Heinz-Peter Schlemmer[2], Matthias C. Roethke[2], Maya Mueller-Wolf[2], Sascha Pahernik[2] and Joseph L. Chin[1]

[1]London Health Sciences Centre, Western University, London, ON, Canada, [2]German Cancer Research Center, University Hospital, Heidelberg, Germany, [3]Beaumont Health System, Royal Oak, MI, USA, and [4]Profound Medical Inc, Toronto, ON, Canada

S.M.N. and G.H. contributed equally towards the data analysis and article preparation.

**Objectives**

To report the 3-year follow-up of a Phase I study of magnetic resonance imaging (MRI)-guided transurethral ultrasound ablation (TULSA) in 30 men with localised prostate cancer. Favourable 12-month safety and ablation precision were previously described.

**Patients and Methods**

As a mandated safety criterion, TULSA was delivered as near whole-gland ablation, applying 3-mm margins sparing 10% of peripheral prostate tissue in 30 men. After 12-month biopsy and MRI, biannual follow-up included prostate-specific antigen (PSA), adverse events (AEs), and functional quality-of-life assessment, with repeat systematic biopsy at 3 years.

**Results**

A 3-year follow-up was completed by 22 patients. Between 1 and 3 years, there were no new serious or severe AEs. Urinary and bowel function remained stable. Erectile function recovered by 1 year and was stable at 3 years. The PSA level decreased 95% to a median (interquartile range) nadir of 0.33 (0.1–0.4) ng/mL, stable to 0.8 (0.4–1.6) ng/mL at 3 years. Serial biopsies identified clinically significant disease in 10/29 men (34%) and any cancer in 17/29 (59%). By 3 years, seven men had recurrence (four histological, three biochemical) and had undergone salvage therapy without complications (including six prostatectomies). At 3 years, three of 22 men refused biopsy, and two of the 22 (9%) had clinically significant disease (one new, one persistent). Predictors of salvage therapy requirement included less extensive ablation coverage and higher PSA nadir.

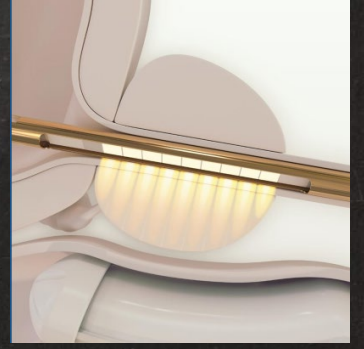
**Conclusion**

With 3-year Phase I follow-up, TULSA demonstrates safe and precise ablation for men with localised prostate cancer.

# Summary of TULSA Literature

- The optimal timing of MRI follow-up seems to be at the earliest at three weeks after treatment, when the post-procedural edema has decreased and the NPV has matured.
- Diffusion-weighted imaging has little or no added diagnostic value in the subacute setting.
- Mäkelä P, Anttinen M, Suomi V, Steiner A, Saunavaara J, Sainio T, Horte A, Taimen P, Boström P, Blanco Sequeiros R. Acute and subacute prostate MRI findings after MRI-guided transurethral ultrasound ablation of prostate cancer. Acta Radiol. 2021

# ADVANTAGES



- Less invasive than cryotherapy, electroporation and laser phototherapy.
- The FUS transurethral route is the best approach to treat the anterior portion of the prostate.
- Perspective of focal cancer treatment
- Relieve of Lower Urinary Tract Symptoms (LUTSs)


- Elterman D, et al. Relief of Lower Urinary Tract Symptoms After MRI-Guided Transurethral Ultrasound Ablation for Localized Prostate Cancer: Subgroup Analyses in Patients with Concurrent Cancer and Benign Prostatic Hyperplasia. J Endourol. 2021

# Advantages

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ARTICLE

## Salvage open radical prostatectomy for recurrent prostate cancer following MRI-guided transurethral ultrasound ablation (TULSA) of the prostate: feasibility and efficacy

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**ABSTRACT**

**Introduction:** MRI-guided transurethral ultrasound ablation (TULSA) is a novel modality for minimally invasive ablation in patients with localised prostate cancer (PCa). A multi-national Phase 1 (30 patients) and subsequent Phase 2 (115 patients) study showed TULSA to be feasible, safe and well tolerated. However, technical viability and safety of salvage prostatectomy for those who failed TULSA is unclear. Herein, we report the feasibility and morbidity of salvage radical prostatectomy (sRP) post-TULSA.

**Methods:** Four patients with biopsy-proven residual cancer following TULSA underwent open retropubic sRP within 39 months of TULSA. Peri-and post-operative morbidity were reported. Detailed histopathologic assessment is reported.

**Results:** Median follow-up was 43 months after sRP. Mean operating times, blood loss, and length of stay were 210 min, 866 ml, and 3.5 days, respectively. Intraoperative finding of some fibrotic reaction of endopelvic and Denonvilliers fascia was characteristic. There were no perioperative complications. Whole-mount pathology sections showed one pT2b and three pT3a, suggesting under-staging pre-TULSA. Location of disease was compatible with persistent cancer mostly in the untreated peripheral safety region. One man received an artificial urinary sphincter. All men experienced erectile dysfunction responsive to treatment. Two patients with positive surgical margins had PSA progression requiring salvage radiation, with one requiring long-term androgen deprivation therapy.

**Conclusions:** RP is a viable and safe salvage option if TULSA fails. Technical difficulty and perioperative morbidity were negligible and attributable to minimal peri-prostatic reaction from TULSA.

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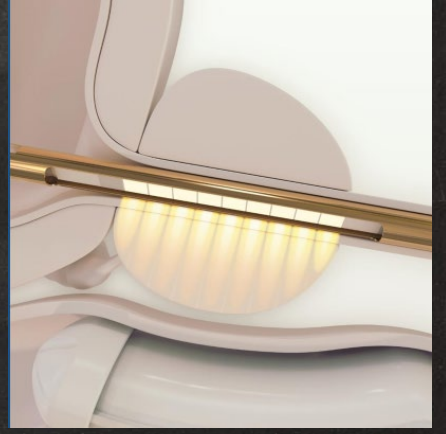
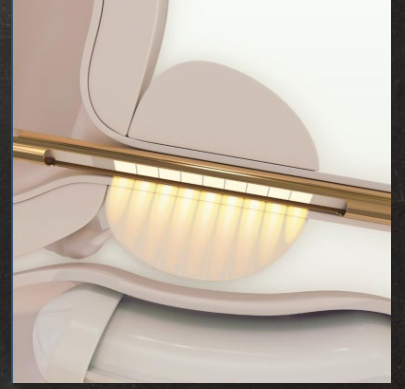
**KEYWORDS**
Salvage prostatectomy; MRI guided; TULSA; localised prostate cancer

# Conclusions



- ✓ TULSA provides minimally invasive thermally-mediated destruction of prostate tissue through directed, non-focused, ultrasound energy
- ✓ Real-time MR-thermometry is continuously acquired during treatment to provide temperature maps useful in adjusting the frequency and power for each transducer element
- ✓ TULSA treatments follow a step-by-step workflow

# Conclusions



- ✓ TULSA is currently indicated for prostate tissue ablation. The pivotal study included patients with localized prostate cancer:
  - ✓ Gleason Grade Group 1-2
  - ✓ Stage ≤T2
  - ✓ PSA ≤15 ng/ml

- ✓ Promising results have been published on TULSA for recurrent and higher-grade cancer and concurrent BPH and cancer

- ✓ Further prospective multicenter trials are warranted to confirm the clinical scenarios that may benefit the most from this emerging technology