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

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4. Department of Urology, Beaumont Health System, Royal Oak MI, United States
5. Profound Medical Inc., Toronto ON, Canada
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

DKFZ Heidelberg, Universitätsklinik Heidelberg
TULSA-PRO DIFFERENCE: ANATOMY

TULSA

Directional Heating

Transurethral Source

Prostate

Rectum

HIFU

Focal Heating

Increased Rectal Contact

Transrectal Source

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TULSA-PRO DIFFERENCE: TREATMENT

TULSA

- Urethral Cooling
- Continuous Heating (Inside-Out)

HIFU

- Discrete Heating (Outside-In)
- Prostate
- Rectum
TULSA-PRO DIFFERENCE: IMAGING

**TULSA MRI-Guided**
- Soft tissue contrast
- Quantitative thermometry
- Temperature feedback control
- Diagnostic
- Limited accessibility

**HIFU Ultrasound-Guided**
- Widely accessible
- Temporal resolution
- Soft tissue contrast
- Diagnostic
- Qualitative feedback
MRI-GUIDANCE

Device Positioning

Precise Treatment Planning

Planning

Temperature Feedback Control

MRI Thermometry Acquisition

Adjust Power, Frequency, Rotation Rate

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
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

Axial T2w MRI

Sagittal T2w MRI

Transurethral Device

Rectal Cooling Device
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

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

IPSS

Box: 25% / Median / 75%
Whiskers: Min / Max within 1.5 IQR
Squares: Average
Circles: Outliers

Pre-Treatment
n = 30

1 month
n = 28

3 months
n = 29

6 months
n = 29

12 months
n = 29

URINARY SYMPTOMS

IPSS Score

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UROFLOWMETRY

Peak Urine Flow

Box: 25% / Median / 75%
Whiskers: Min / Max within 1.5 IQR
Squares: Average
Circles: Outliers

Pre-Treatment
n = 30

1 month
n = 28

3 months
n = 26

6 months
n = 29

12 months
n = 29

p = 0.22
ERECTILE FUNCTION

IIEF-15 Erectile Function Domain

Pre-Treatment
n = 29

1 month
n = 28

3 months
n = 29

6 months
n = 30

12 months
n = 29

IIEF-15 EF Domain Score

Box: 25% / Median / 75%
Whiskers: Min / Max within 1.5 IQR
Squares: Average
Circles: Outliers

p=0.62
BOWEL HABITS

UCLA-PCI-SF Bowel Habits Domain

Box: 25% / Median / 75%
Whiskers: Min / Max within 1.5 IQR
Squares: Average
Circles: Outliers

Pre-Treatment: n = 30
1 month: n = 28
3 months: n = 29
6 months: n = 30
12 months: n = 29

p = 0.90
ABLATION EFFICACY

Pre-Treatment
n = 30

1 month
n = 30

3 months
n = 28

6 months
n = 30

12 months
n = 30

PSA (ng/ml)

Box: 25% / Median / 75%
Whiskers: Min / Max within 1.5 IQR
Squares: Average
Circles: Outliers

p<0.0001
BIOPSY RESULTS AT 12 MONTHS

Phase I treatment parameters were conservative
- First-in-human study as primary treatment for prostate cancer
- Lethal thermal dose \( -0.7 \pm 1.2 \text{ mm inside prostate} \)
- 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

Phase I Parameters → Pivotal Trial Parameters

- Thermal-dose boundary: -0.7 ± 1.2 mm inside prostate boundary
- Thermal-dose boundary: 1.5 ± 1.2 mm outside prostate boundary
**Acute H&E Histology**

- 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

* Courtesy Rajiv Chopra

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