Prostate Cancer in the Era of Focal Therapy: Is Image Guided Therapy Effective?

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Disclosures

EDAP TMS, Inc.
Principal Investigator and Consultant
High Intensity Focused Ultrasound

- Heat effects on tissue known throughout history
- Coagulation effects begin with temperature of 60°C
- Focused ultrasound waves may raise core tissue temperature to 85°C at focal point
- Gradient of temperature protects adjacent tissues and organs
Advantages of HIFU:

- Non-invasive surgery
- Repeated treatment
- Palliative therapy

$I_{SPTA} > 1,000 \text{ W/cm}^2$
HIFU

• Indications for use in GU cancers:
  • Kidney cancer:
    – Small renal masses
  • Prostate cancer:
    – Radiation failure salvage therapy
    – Primary cancer treatment
The Common Foundation of All HIFU Devices

- Focusing a beam of high intensity ultrasound waves can result in the ablation of a discrete volume of tissue
- The desired effect: Heating
  - Lipid membranes melt
  - Proteins denature
- Persona non grata: Cavitation
  - Air bubbles cause reflection of the US beam
  - Cavitation the consistency of ablation volume
Prostate Transrectal HIFU: Basic Engineering Goal

• Create a device that:
  – Fits into the rectum
  – Renders a high quality image for planning
  – Creates high quality and reproducible ablation volumes
  – Avoids cavitation
Safety features

Ablatherm
- Rectal wall cooling
- Rectal wall temperature monitoring
- Rectal wall distance measurement
- Infrared movement detection

Sonablate
- Rectal wall cooling
- Rectal wall temperature monitoring
- Rectal wall distance measurement
- Visual Movement detection
- Reflectivity measurement

EDAP TMS
Lesion Size

Ablatherm

- 19-24 mm focal length
- Allows for treatment with one pass
- Larger prostates can be downsized with hormones or per op TURP

Sonablate

- 10 mm focal length
- Multiple passes needed for treatment
- Allows for enhanced conformity
History of HIFU development

• 1989: Start of technical development and animal experiments
• 1990: Dunning tumor studies
• 1991: Endorectal applicator test in rabbit prostates
• 1992: BPH treatment as first human HIFU treatment
• 1993: PCa treatment with adapted treatment parameters

• 1995: from prototype to serial device
• 1995: European PCa Multicenter study
• 2000: CE labeling of Ablatherm® with TUR before HIFU-
• 2003: 26 hospitals > 4,000 treatments
• 2013: > 250 hospitals, > 30,000 treatments worldwide

Therapeutic Ultrasound Research Laboratory, Université de Lyon, INSERM, U556, Lyon, France
Department of Urology, Edouard Herriot Hospital, Lyon, France
Klinikum Harlaching, Munich, Germany
EDAP TMS Inc., Lyon, France
HIFU and Prostate Cancer
European Multicenter Study

risk groups

**low risk (31.2 %)**
T1 - T2a and PSA ≤ 10 ng/ml and Gleason ≤ 6

**middle risk (48.2 %)**
T2b or PSA 10.1-20 ng/ml or Gleason = 7

**high risk (20.6 %)**
T2c or PSA > 20 ng/ml or Gleason ≥ 8

negative biopsies

86.2 %
Nadir PSA 0.40 ng/ml

81.8 %
Nadir PSA 0.26 ng/ml

72.1 %
Nadir PSA 0.27 ng/ml

Thueroff, S., Chaussy, C., Vallancien,G. et al., J Endourol. 2003; 17:673-677
Munich data update
maximum 14 years follow up (n = 702)

High Risk Prostate Cancer

• Adjuvant radiation therapy in high risk prostate cancer may be beneficial..yet..
• Focally positive margin patients exhibited similar failure patterns as negative margin patients in the control group of the EORTC randomized trial of adjuvant radiation therapy

Clinical or biological PFS

Extracapsular extension

Number of patients at risk:

| O  | N  | Number of patients at risk:
|----|----|----------------------
| 40 | 124| 101                  |
| 14 | 36 | 30                   |
| 64 | 118| 79                   |

p = 0.0006

Focal

Extensive

Negative

(years)
ENLIGHT Clinical Trial in Low Risk, Low Stage Prostate Cancer 2006 - 2014

USA FDA IDE: G050103

135 HIFU subjects enrolled at 13 sites in the USA and 1 in Canada

D’Amico Low risk patients only

No previous PCa treatment

HIFU Performed without TURP
Efficacy of High Intensity Focused Ultrasound (HIFU) as a Primary Monotherapy for Low Risk Localized Prostate Cancer: Outcomes from the ENLIGHT Trial


ABSTRACT

Between 2007 and 2010 transrectal ultrasound guided high intensity focused ultrasound (HIFU) was employed in a FDA approved IDE registration clinical trial (ENLIGHT Trial) in men with low grade, low risk prostate cancer. Efficacy outcomes are reported.

INTRODUCTION

High intensity focused ultrasound utilized Ablatherm® Integrated imaging (EDAP Technomed, Lyon, France). Subjects were administered either spinal or general anesthesia. The subject was positioned on the treatment module (table) in a right decubitus manner. A single endorectal probe capable of both ultrasonography and treatment HIFU was carefully inserted into the rectal cavity after manual dilation of the rectal sphincter to accept three fingers. Ultrasound imaging was used to detect the contour of the prostate and the target treatment volume was defined on the computer screen. Treatment volume encompassed greater than 100% of the prostate volume. Under robotic control, the treatment delivery head was systematically moved within the endorectal probe to deliver HIFU energy in consecutive blocks defined by the operating surgeon using computer planning software. A 4mm margin of safety at the prostatic apex remained untreated. After the prescribed treatment volume was completed, bladder drainage was provided through in-dwelling urethral Foley catheter or suprapubic tube. All patients subjects were prescribed a course of prophylactic antibiotics. Patients were either discharged the same day or remained overnight.

PROCEDURE

Table 1: Biopsy Results per Core

Table 2: Prostate Volume Post-HIFU at First Biopsy

RESULTS

For cause biopsy was performed in the event of three consecutive rises in PSA regardless of magnitude. An end of study biopsy, regardless of PSA was included in the 24-month visit. During each prostate biopsy session, multiple, systematic random cores were obtained using standard transrectal ultrasound guided technique. Two biopsy rates were calculated: the per core negative biopsy rate and the biopsy survival rate. The per core negative biopsy rate reports the number of positive cores by discrete location and thus is a more sensitive indicator of effective tissue ablation than the biopsy survival rate, which reports a subject as a failure if only 1 core is positive and the rest (typically 1-9) are negative. The per core negative biopsy rate is calculated by subtracting the percentage of biopsy cores which are positive from 100.

Table 3: Adverse Events

For cause biopsy was performed in the event of three consecutive rises in PSA regardless of magnitude. An end of study biopsy, regardless of PSA was included in the 24-month visit. During each prostate biopsy session, multiple, systematic random cores were obtained using standard transrectal ultrasound guided technique. Two biopsy rates were calculated: the per core negative biopsy rate and the biopsy survival rate. The per core negative biopsy rate reports the number of positive cores by discrete location and thus is a more sensitive indicator of effective tissue ablation than the biopsy survival rate, which reports a subject as a failure if only 1 core is positive and the rest (typically 1-9) are negative. The per core negative biopsy rate is calculated by subtracting the percentage of biopsy cores which are positive from 100.

Per Core Negative Biopsy Rate = 100 - %Positive Cores

The Biopsy Survival rate is calculated by subtracting the percentage of subjects with positive biopsy findings from 100:

Biopsy Survival Rate = 100 - %Subjects with Positive Biopsy

REFERENCES


Source of Funding: EDAP TMS, Inc.
<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
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</thead>
<tbody>
<tr>
<td>Baseline Volume</td>
<td>134</td>
<td>22.7</td>
<td>12.5</td>
<td>21.6</td>
<td>9.7</td>
<td>152.0</td>
</tr>
<tr>
<td>First post-HIFU Biopsy (with volume):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (cc)</td>
<td>113</td>
<td>9.0</td>
<td>6.3</td>
<td>7.8</td>
<td>1.2</td>
<td>33.0</td>
</tr>
<tr>
<td>Volume change from Baseline (cc)</td>
<td>112\textsuperscript{1}</td>
<td>-13.6\textsuperscript{2}</td>
<td>14.4</td>
<td>-12.7</td>
<td>-145.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Visit</td>
<td># Cores</td>
<td># Positive</td>
<td>% Positive</td>
<td>Per Core Negative Biopsy Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
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<td>------------</td>
<td>------------</td>
<td>-------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1251</td>
<td>365</td>
<td>29.2%</td>
<td>70.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up (Unscheduled and/or Month 24 Overall)</td>
<td>1127</td>
<td>87</td>
<td>7.7%</td>
<td>92.3%</td>
<td></td>
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</tbody>
</table>

Increase in Per Core Negative Biopsy Rate from baseline is statistically significant at p<0.0001
Morbidity of High Intensity Focused Ultrasound (HIFU) as a Primary Monotherapy for Low-Risk Localized Prostate Cancer: Outcomes from the ENLIGHT Trial

Potency
(UCLA-PCI Questionnaire)

Potency (of those potent at Tx)

<table>
<thead>
<tr>
<th></th>
<th>One Year</th>
<th>Two Years</th>
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</thead>
<tbody>
<tr>
<td>Full recovery (sufficient for penetration)</td>
<td>24.1%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Partial recovery</td>
<td>35.1%</td>
<td>24.3%</td>
</tr>
</tbody>
</table>
Continence

% return to baseline (p>0.05) @ 24 months
High Intensity Focused Ultrasound (HIFU) Clinical Approvals

• FDA approval 10/2015 for the treatment of prostate tissue ablation with HIFU
• Focused ultrasound is currently available in the US to treat uterine fibroids and essential tremor.
• The option for non-invasive treatment of prostate cancer in an ambulatory surgery setting is a significant step forward for patients.
Monofocal tumor, treated with safety margin
Focal Therapy of GU Malignancies

• Imaging dependent technology
• Tissue destructive technique
• Cancer detection pre- and post-treatment feasible and reproducible
• Re-treatment an option for treatment failures
Focal Therapy of GU Malignancies

- Cryotherapy
- High Intensity Focused Ultrasound
- Interstitial Laser Therapy
- Photodynamic Laser Therapy
Cryotherapy

- Tissue ablation at the time of 2 freeze/thaw cycles
- Immediate pathology reveals cell ghosts
- Tissue sloughing, fibrosis and shrinkage occurs over 3-6 months
- Urethral preservation with warming catheter
- Tissue effects dramatic on US, CT, MRI
High Intensity Focused Ultrasound

- Heat effects on tissue known throughout history
- Coagulation effects begin with temperature of 60 °C
- Focused ultrasound waves may raise core tissue temperature to 85 °C at focal point
- Gradient of temperature protects adjacent tissues and organs
Focal therapy

- Focal Cryoablation
- High-Intensity Focused Ultrasound
- NanoKnife®
- Vascular Targeted Photodynamic Therapy

International Symposium on Focal Therapy and Imaging in Prostate & Kidney Cancer
Imaging Techniques

• Transrectal Ultrasound
  – Cryotherapy
  – HIFU
  – Photodynamic Laser Therapy

• Magnetic Resonance Imaging
  – Interstitial Laser Therapy
  – HIFU
Duke Clinical Opportunities

– Clinical Lead (Cary Robertson, Tom Polascik)
  • Integrate Cryotherapy/HIFU into Duke’s prostate cancer management options by routing patients requesting HIFU through the Multi-D Clinic, thereby ensuring that the patients will receive appropriate treatment and that all service lines have the opportunity to interact with these patients
  • Develop algorithms for patient selection and eligibility for HIFU. Provide leadership nationally in the proper application of HIFU in localized prostate cancer.
  • Coordinate HIFU with existing programs of Active Surveillance, Radiation Therapy, Surgery and Cryotherapy for localized prostate cancer.
  • Build on prior experience with cryoablation, recognizing the leadership role of Duke in the area of Focal Therapy nationally and internationally
  • Radiation Oncology (Bridget Koontz, Robert Lee) partnership across therapies for salvage and potentially primary disease
Focal Therapy of GU Malignancies

- Duke Cancer Institute offers single site coordinated care of cancer patients combined with consultative services for survivorship care.
- The Division of Urology supports the patient care mission of Duke Medical Center with innovative research.
- Collaborative efforts across the university expands the potential of basic and clinical research.
Duke Research in HIFU

- Initiatives:
  - Biomedical Engineering collaboration for device development - Cary Robertson/Pei Zhong – animal models of HIFU and immunotherapy
  - Basic Science (Brant Inman, Bridget Koontz) – review immuno-modulating response
  - Clinical Science (Tom Polascik) – thermally based treatment comparisons
  - Imaging - pre and post HIFU MRI monitoring (Raj Gupta/Tom Polascik/Cary Robertson)
  - Outcomes - Compare whole gland ablation to partial ablation or hemi-ablation of the prostate gland
  - Clinical Registry
  - Survivorship Clinic as and essential component of patient management (Drew Peterson)
Our Team

An Interdisciplinary and Translational Research Group

Pei Zhong, Ph.D.
Biomedical Engineering

Hui-Wen Lo, Ph.D.
Cancer Biology

Cary Robertson, M.D.
Urologic Surgery

Mari Shinohara, M.D.
Immunology
Preliminary Results

B - scan ultrasound image of tumors during HIFU treatment, indicating cavitation activities in tumor tissues (arrow points to region of hyperechogenicity)

Photographs of excised tumors after HIFU treatment, showing regions of mechanical damage by cavitation bubbles
Preliminary Results

- No recurrent tumor growth in both groups after surgery

Growth curves for re-challenged tumors

Animal survival rates after re-challenge
Ablation combined with immunotherapy: a new paradigm for prostate cancer?
Future Directions

– Second generation technology accessibility
  • Fusion imaging and targeted treatment of small volume intermediate or high risk lesions as early as 2017 (Focal 1 Device)(Uronav/Sonacare)

– Education and Training
  • East Coast training site for providers
  • National Center of Excellence
  • Standard of Care Development and Thought Leadership
The future of HIFU is evolving but extremely important, not only as a primary therapy but also as an adjunct to additional strategies i.e. immunotherapy.

HIFU Natural History Hypothesis testing in active surveillance populations will require long term studies.

Focal HIFU will be the ideal strategy for such low morbidity treatments and will allow attractive randomization schemes.